An evaluation of Western Herbal Complementary Medicine labelling in South Africa, to determine whether the product labelling information complies with established herbal monographs and whether it meets local regulatory requirements

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Title

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Abstract

INTRODUCTION

Complementary Medicines (CMs) are widely available to the South African public. However, CMs have not yet been evaluated by the Medicines Control Council (MCC). The MCC has published new guidelines for the regulation of CMs, with which CM companies are required to comply.

OBJECTIVE

Determine to what degree Western Herbal CM labelling complies with the MCC's requirements.

METHODS

Thirteen CM products containing recognised Western Herbal ingredients were selected from pharmacies in the northern suburbs of Johannesburg. Labelling information on the immediate and outer container labels, as well as the package inserts, was investigated. The relevant corresponding European Medicines Agency (EMA) monographs and MCC guidelines were used to assess compliance.

RESULTS

None of the products complied with the product dosage section of the monographs. Furthermore, the products contained indications that were not present in the monographs. The products did not fully meet the MCC's mandatory minimum

labelling requirements, and they did not demonstrate total compliance with all of the MCC's requirements for product labels and package inserts.

CONCLUSION

CM labelling is not fully compliant with the MCC's requirements, and is required to undergo improvement in order to achieve MCC regulatory compliance.

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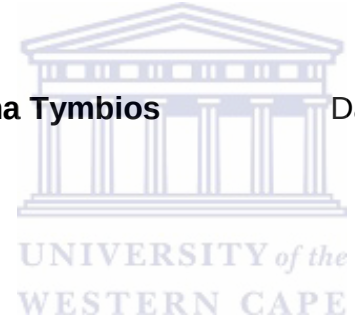
Declaration

I declare that this thesis that I now submit for assessment on the programme of study leading to the degree Master of Science in Pharmacy Administration and Policy Regulation has not been submitted for the purpose of a degree at this or any other higher education institution. It is entirely my own work and has not been taken from the work of others, save the extent that such work has been cited and acknowledged within the text of my work. I agree to deposit this thesis in Hibernia College's institutional repository and the University of Western Cape's library or allow the library to do so on my behalf, subject to Irish and South African Copyright Legislation and Hibernia College Libraries and the University of Western Cape's conditions of use and acknowledgement.



Signed**:** **Joanna Tymbios** Dated: **13 November 2015**

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List of Abbreviations

Act 101 of 1965	Medicines and Related Substances Act, 1965 (Act No. 101 of 1965), as amended
AHPCSA	Allied Health Professions Council of South Africa
CAMs	Complementary and Alternative Medicines
CEC	Clinical Excellence Commission
CMs	Complementary Medicines
EMA	European Medicines Agency
EU	European Union
GMP	Good Manufacturing Practice
GPP	Good Pharmacy Practice
MCC	Medicines Control Council
SAPC	South African Pharmacy Council
WHO	World Health Organisation

Chapters

1 Introduction

The R8-billion Complementary Medicine (CM) industry (Kahn, 2015) is thriving in South Africa. CM is a broad term used to describe medicine practices that fall outside of the orthodox medicine system. The World Health Organisation (WHO) groups "Complementary/Alternative" Medicines, and describes these as practices that are not part of the country's leading health care structure, and are also not part of the country's traditional medicine (WHO, 2016). The WHO further describes that the terms "complementary" and "alternative" may be used interchangeably with traditional medicine in certain countries (WHO, 2016).

The South African Minister of Health, together with the Medicines Control Council (MCC), defines CMs as medicines which originate from plants, animals or minerals, and are associated with the innate healing power of a human or animal (MCC, 2013c). Furthermore CMs are associated with the disciplines practiced by members of the Allied Health Professions Council of South Africa (AHPCSA) (MCC, 2013c). Examples of these disciplines include: Homoeopathy, Western Herbal Medicine and Traditional Chinese medicines (MCC, 2013a).

In South Africa, traditional-use medicines are associated with African Traditional Medicine. The regulation of African Traditional medicines falls out of the scope of the CM regulations, as these apply only to disciplines associated with the AHPCSA (MCC,

2013a). Traditional medicine is associated with traditional philosophy, which encompasses indigenous African beliefs (Government Gazette, 2008).

Despite the fact that CMs are widely used by the South African public (MCC, 2013a), CM regulation has not been fully implemented. The AHPCSA was established in 1982 to regulate Allied Health Professionals (AHPCSA, 2015). However, the associated CMs for the AHPCSA disciplines have not yet been regulated.

There is a false perception that CMs are safe, as they are “natural” (Health24, 2015). While orthodox medicines are not always of a “natural” origin they are required to demonstrate quality, safety and efficacy in order to be approved for use. Therefore, they must be produced in compliance with Good Manufacturing Practice (GMP) as stipulated by the South African Medicines Control Council (MCC) (MCC, 2010). Furthermore, safety and efficacy are required to be demonstrated through appropriate clinical studies (MCC, 2013a). CMs have not yet undergone the strict regulatory evaluation and approval that orthodox medicines undergo; therefore they may not contain the active ingredients that the labelling states they do, or they may contain potentially toxic ingredients. Any claims pertaining to quality, safety and efficacy have not been substantiated, and this poses a threat to public health.

The MCC recognised that CMs are widely consumed yet unregulated, and they published Complementary and Alternative Medicines (CAMs) guidelines in 2013 (MCC, 2013a). The guidelines specify what data is required to prove quality, safety and efficacy. Adhering to these guidelines poses a challenge to the CM industry, and in turn

to the MCC, which is the authority responsible for evaluating the data submissions. The CM industry faces having their products withdrawn from the market if they do not comply with the MCC's regulations, and will need to invest a significant amount of resources to obtain MCC approval.

This research project aims to provide information regarding the regulatory compliance of CMs currently available on the market. An important medicine regulation requirement pertains to appropriate product labelling. This is intended to provide consumers with information on how to use the product correctly to achieve efficacy, as well as provide important safety information such as warnings and contra-indications. The compliance of product labelling with regard to MCC requirements is investigated in this study.

All CMs were mandated to comply with a specific set of minimum labelling requirements by 15 May 2014 (MCC, 2013b), and the achievement thereof will be determined in this research project. The study area is Western Herbal medicine, a CM discipline recognised by the MCC (MCC, 2013a). This is a significant discipline to study, as it has been approximated that almost 27% of the public consumes herbal medicines (Health24, 2015). Specifically, Western Herbals promoted for immune-enhancing effects will be studied. The MCC has created an appropriate category, "immune boosters", for these CMs, and they are required to be submitted for registration by May 2016 (MCC, 2013c).

Immune boosters are often promoted for conditions such as the common cold. This is the most frequently occurring disease in humans (Van Schoor, 2014, p.14), and a likely

condition for which consumers will seek treatment. Therefore, immune boosters are a relevant category to study.

Further relevance of the study of immune boosters is that immune boosters have the potential to be classified as high risk medicines. The Clinical Excellence Commission (CEC) of Australia (2016) defines high risk medicines as those that “have a high risk of causing injury or harm if they are misused or used in error” (CEC, 2016). Patients seeking treatment for a wide range of life-threatening diseases, such as HIV, TB or other infectious diseases that require effective orthodox therapies, may select and misuse an immune booster for their illness. The use of such inappropriate therapies will likely result in illnesses remaining untreated and progressing to a further deterioration in health, and possible death.

2 Literature Review

2.1 Complementary Medicine Regulation – a History in South Africa

Historically, CMs were not required to undergo the strict regulatory approval process that orthodox medicines are subjected to. As a result, many products on the market are not MCC-approved as they have not been evaluated. In 2002 the MCC communicated, through a notice in the Government Gazette (No. 7282 R. 204), that CM companies were required to furnish the MCC with information regarding marketed products as well as those about to enter the market (MCC, 2013b). This enabled the MCC to conduct an audit regarding the status of CMs available to the public at the time (MCC, 2013b). This

was achieved through notifications submitted by CM companies (MCC, 2013b). Applicants were provided with a complementary registry number, which served to confirm that the notification had been received, but had not been evaluated or registered.

While these notifications provided limited information, they were not registration applications and could not be assumed to be such (MCC, 2013b). Since the MCC was reliant upon companies providing them with the notification information, there was the potential for some companies not to comply. Therefore, the notification process needed to evolve into a set of clear guidelines.

In July 2011 the Minister of Health proposed that the Regulations to the Medicines and Related Substances Act No. 101 of 1965 (hereafter referred to as Act 101 of 1965), were amended to include CMs (MCC, 2013b). CMs were allocated a specific medicine category, Category D, pertaining to CMs ready for use in humans and animals (MCC, 2011). Amendments to labelling requirements were also proposed during this process (MCC, 2011).

This proposal was updated and published in its final, legally-binding form in November 2013 (MCC, 2013c). In December 2013, the MCC published guidelines relating to the regulatory requirements of CMs. These included one set of guidelines relating to the quality, safety and efficacy of CMs, and another comprising a roadmap for the implementation thereof (MCC, 2013a, 2013b). An important component of both sets of guidelines pertains to labelling requirements.

The MCC prescribes that if a current CM falls within one of the CM pharmacological categories it is required to be submitted for registration (MCC, 2013c), a mere amendment in the current medical claim is not permitted. No medicinal claims may be made, and the mandatory disclaimer is required to be present on the product label, package insert and patient information leaflet (MCC, 2013c).

In September 2014, further amendments to Act 101 of 1965 were proposed and published for comment in Government Notice No. 37995 (MCC, 2014) These proposed changes to the current definition of a CM, by expanding from where a CM could originate, and the indications for CMs such as the inclusion for diagnosis and treatment.

2.1.1 Western Herbal Medicines

For a product to be classified as a CM, it must fit the MCC's definition thereof. Western Herbals meet this definition. They originate from plants, contribute to the human being's innate healing ability, and fall under the scope of Phytotherapy.

Phytotherapy is a discipline registered under the Allied Health Professions Act No. 63 of 1982 (MCC, 2013a). The MCC recognises herbal substances that are referenced as such in formal literature, such as EMA community herbal monographs, Australian Therapeutic Goods Authority List of Substances, the German Commission C Monograph, the WHO monographs on Selected Medicinal Plants or British Herbal Pharmacopoeia, to name a few (MCC, 2013a).

2.1.2 Labelling Requirements

CMs were required to comply with specific minimum labelling requirements by 15 May 2014 (MCC, 2013b). Requirements included that the labelling appear in English and at least one other official language. Furthermore the label had to state the category of medicine, the pharmacological classification, the discipline of the medicine, and the statement: “This medicine has not been evaluated by the Medicines Control Council. This medicine is not intended to diagnose, treat, cure or prevent any disease.” (MCC, 2013b). The complete labelling requirements for CMs are prescribed in Regulations 8, 9 and 10 of Act 101 of 1965 (MCC, 2013b). Regulation 8 pertains to the product label, Regulation 9 to the package insert, and Regulation 10 to the patient information leaflet (MCC, 2013b).

2.2 Regulation of Western Herbal Medicinal Products in the European Union

The EMA requires that Western Herbals undergo regulatory approval. There are three options available when applying for marketing authorisation for these products (EMA, 2014b). The application may be submitted as (1) a full application, (2) a well-established use, or (3) a traditional use (EMA, 2014b). A full application is required for a new herbal product, while a well-established application is used for herbal ingredients with ten years of proven medicinal use in the European Union (EU). Traditional use applies to products that have been in use for thirty years (EMA, 2014b).

For all three routes, the application must meet full quality requirements (EMA, 2014b). New applications require non-clinical data to demonstrate safety, and clinical trial data to demonstrate efficacy (EMA, 2014b). For both safety and efficacy, bibliographical data is acceptable for well-established use applications (EMA, 2014b). The safety and efficacy requirements for traditional-use applications are the least stringent. A bibliographical expert report may justify safety, while efficacy may be motivated using long-standing experience (EMA, 2014b). However, products that undergo the traditional-use approval pathway have restrictions on the product indications: that the product is non-prescription and may not be indicated for serious or chronic conditions such as cancer or diabetes (EMA, 2014b). Furthermore, traditional-use products may not be indicated for influenza (EMA, 2014b).

2.3 European Medicines Agency Herbal Monographs

The EMA monograph has undergone review and approval by the EMA's Committee on Herbal Medicinal Products (EMA, 2015). The monograph contains information relating to the product's safety and efficacy, and describes what the product should be used for (EMA, 2015). While there are other recognised monographs from which to select, for the limited scope of this research project the EMA monograph will be used as the reference tool to assess the selected products' labelling regarding quality, safety and efficacy.

2.4 The Industry's Perspective

The new legislative requirements have not been well received by various industry stakeholders in South Africa. It is estimated that 80% of CM products available on the market risk being withdrawn if they cannot meet the MCC's requirements (Kahn, 2015). Therefore, CM companies are required to invest large sums of money in an effort to obtain the data required for product registration. Should the companies fail in this regard, they face the considerable financial loss of product withdrawal.

The new regulations place an additional expectation on the CM industry, as well as on pharmacies, which are also seen to be in violation of the law if they sell non-compliant products (Kahn, 2015). Pharmacies and Pharmacists are governed by the South African Pharmacy Council (SAPC) and are required to obey the Pharmacy Act No. 53 of 1974 as well as Good Pharmacy Practice, which is prescribed by the SAPC (SAPC, 2010). An important component of this is that pharmacists should not sell medicines for which they cannot confirm the quality, safety and efficacy (SAPC, 2010). Since CMs have not been MCC-approved, pharmacists selling CMs could be seen to be in violation of GPP. However, while pharmacies are governed by applicable laws, the law currently does not affect health shops, which in theory could continue to sell unapproved CM products.

While the new requirements do place additional strain on the CM industry, the MCC has a responsibility to enforce these requirements. The MCC has been criticised for not having acted swiftly enough to control the availability of CMs. The MCC's duty is to protect public health, and if available CMs have not been MCC-evaluated – at the very

least for quality – the public remains at risk of consuming unsafe and ineffective medicines (Jobson, 2009, p.511).

3 Methodology

A qualitative, descriptive study design was selected to collect and analyse the data, which was in the form of text presented on CM products available in South African pharmacies and health shops.

3.1 Study Setting

The demographic area chosen for this study was the northern suburbs of Johannesburg. This area was selected as it was likely to provide a large variety of the required CM products that cater to its affluent population. Statistics South Africa (2015) denotes Johannesburg as the largest city in South Africa and the capital of the country's wealthiest province, Gauteng. As the country's economic hub, Johannesburg has a large retail market with a broad scope of products to purchase. The city's northern suburbs are in close proximity to the Sandton central business district. The City of Johannesburg (2015) describes the majority of this population as highly educated, well-paid professionals. There is a wide selection of large-chain pharmacies in this area, as well as smaller, privately owned pharmacies and health shops. These pharmacies contain a wide selection of the various marketed brands of Western Herbal Medicines

and provided a broad sample of the immune-boosting Western Herbals required for this study.

The study setting included major shopping malls and smaller suburban shopping centres in the suburbs of Killarney, Parkview, Hyde Park, Hurlingham, Bryanston and Benmore, so as to include as broad a scope of different outlets as possible. These are illustrated in the map below, which shows the proximity of these suburbs to the Sandton CBD (Figure 3-1).

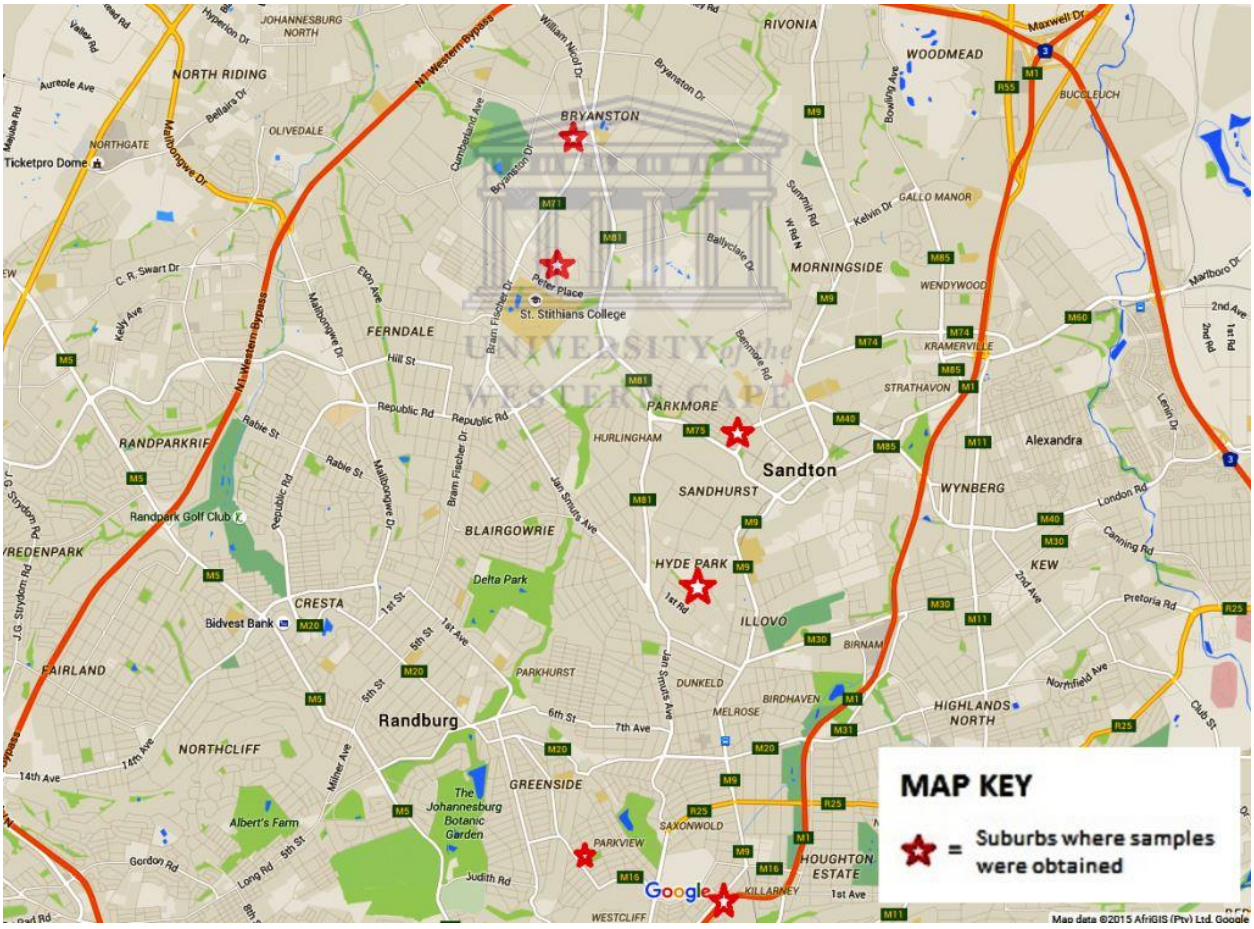

Figure 3-1 A map of the northern suburbs of Johannesburg which comprised the areas for sampling of products.

3.2 Sampling

The unit of analysis was the individual CM product. The sampling was non-random and used purposive sampling. Products were selected using two inclusion criteria. The first was that product labelling contained claims indicating that the product could be used for immune-enhancing effects, as this is the study's focus area. The second criterion was that the product contained one or more Western Herbal ingredients listed in the EMA monographs, as these are recognised as herbal medicines by the MCC (MCC, 2013a). Only one recognised body's monograph was selected, based on the scope of this study. The EMA monographs were selected as the comparative monographs, as they provided comprehensive data and were readily available on the EMA website. Products specifically indicated for paediatric use were excluded from the sample, as the EMA monographs did not contain sufficient data on studies conducted in the paediatric population.

3.3 Data Collection

A qualitative data collection tool, in the form of a labelling assessment form, was created based on the product-specific EMA monograph, the MCC minimum requirements, and the labelling requirements of Act 101 of 1965. The template of this form can be found in Appendix 2.

The data collection tool has three parts. The first contains a comparison of the product's labelling with the information prescribed in the corresponding EMA herbal monograph. This was used to determine whether the product's immediate and outer container

labels, as well as its package insert, contained accurate information pertaining to the quality, safety and efficacy sections of the monograph. The monograph was selected to be in the first part of the tool, as the information obtained from this section would be used to assess compliance in the two parts that followed.

The EMEA monograph was used because it has undergone extensive review and approval by the EMA's Committee on Herbal Medicinal Products (EMA, 2015), and therefore is a valuable reference tool with which to compare the information presented on the studied products. The monographs were easily located on the EMA website, and provided comprehensive data with which to compare the study products. Table 3-1 indicates which of the headings contained in the EMA monograph correspond to quality, safety or efficacy information. Posology is a term used by the EMA to describe the dosage and dosage frequency.

Table 3-1 Headings of the European Medicines Agency monograph that correspond to quality, safety and efficacy of medicines on the product label and package insert.

Monograph heading	Corresponding aspect of quality, safety and efficacy	Where this is found on medication
Qualitative and quantitative composition	**Quality**	Immediate label, outer label, package insert
Pharmaceutical form		Immediate label, outer label, package insert
Therapeutic indications	**Efficacy**	Immediate label, outer label, package insert
Posology		Immediate label, outer label, package insert
Duration of use		Immediate label, outer label,

		package insert
Method of administration		Immediate label, outer label, package insert
Contra-indications	**Safety**	Package insert
Special warnings and precautions for use		Immediate label, outer label, package insert
Interactions with other medicinal products and other forms of interaction		Package insert
Pregnancy and lactation		Immediate label, outer label, package insert
Effects on ability to drive and use machines		Package insert
Undesirable effects		Package insert
Overdose		Package insert

The second part of the data collection tool was used to assess whether the product labelling satisfied the MCC's minimum prescribed information requirements, which should have been implemented by 15 May 2014 (MCC, 2013). This was chosen to be the second part, since the information required is mandatory and provides a direct conclusion regarding compliance or lack thereof.

The third part of the data collection tool was used to assess whether the product labelling complied with the requirements of Regulations 8, 9 and 10 of Act 101 of 1965. These are the requirements for the labels on the immediate and the outer container (carton), the package insert, and the patient information leaflet. The requirements for the immediate container label and outer container label are presented in Table 3-2. The requirements for the package insert and patient information leaflet are presented in Table 3-3.

Table 3-2 Information required for immediate container label and outer container label of medicine according to Regulation 8 of Act 101 of 1965.

Requirement	Immediate container label	Outer container label
Clearly legible indelible letters in English	Required	Required
Clearly legible indelible letters in at least one other official language	Required	Required
Scheduling status (where applicable)	Required	Required
Proprietary name of the medicine	Required	Required
Registration / reference number	Required	Required
Dosage form	Required	Required
Approved name of each active ingredient of the medicine	Required	Required
Quantity thereof contained in a dosage unit, or per suitable mass or volume or unit	Required	Required
Name and percentage of any bacteriostatic or bactericidal agent which has been added to the medicine as a preservative	Required	Required
Approved name of any anti-oxidant contained in the medicine	Required	Required
Quantity of sugar contained in the medicine	Required	Required
Quantity of ethyl alcohol contained in the medicine, expressed as a percentage of the total volume of the medicine if such quantity exceeds two per cent by volume	Required	Required
Content of the medicine package expressed in the appropriate unit or volume of the medicine	Required	Required
Approved indications for use of the medicine	Required	Required
Recommended dosage of the medicine	Required	Required
Where applicable, the instruction 'Shake the bottle before use'	Required	Required
Lot number	Required	Required
Expiry date	Required	Required
Name of the holder of certificate of registration (or name of applicant)	Required	Required
Storage temperature and other precautions required for the preservation of the medicine	Required	Required
The warning: 'Keep out of reach of children'	Required	Required

Table 3-3 Requirements for the package insert and patient information leaflet according to regulation 9 and 10 of Act 101 of 1965.

Package insert	**Patient information leaflet**
Clearly legible text in English	Information in English
Clearly legible text in at least one other official language	Information in at least one other official language
Scheduling status (where applicable)	Scheduling status
Proprietary name and dosage form	Proprietary name and dosage form
The approved name of each active ingredient Quantity thereof contained in a dosage unit or per suitable mass or volume or unit of the medicine	Composition of the medicine (information contemplated in Regulation 9)
The approved name and quantity of any bactericidal or bacteriostatic agent included in the medicine as a preservative, expressed as a percentage	
The quantity of ethyl alcohol included in a preparation for oral or parenteral administration, if such quantity exceeds two per cent by volume	
The words "contains TARTRAZINE" should the medicine contain such ingredient	
"contains sugar" or "sugar free" whichever is applicable	
Pharmacological classification	
Pharmacological action	
Indications	The approved indications and use Instructions on how to take the medicine, including the following statement: "Do not share medicines prescribed for you with any other person."

Package insert	**Patient information leaflet**
Contra-indications	Contra-indications
Warnings	Warnings
Interactions	Interactions The statement: "If you are taking medicines on a regular basis, using the medicine at the same time with another medicine may cause undesirable interactions. Please consult your doctor, pharmacist or other health care professional for advice."
Pregnancy and lactation	The statement: “If you are pregnant or breast-feeding your baby while taking this medicine please consult your doctor, pharmacist or other health care professional for advice.”
Dosage and directions for use	Instructions on how to take the medicine, including the following statements: "Do not share medicines prescribed for you with any other person." "In the event of over dosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre”
Side effects and special precautions	Precautions Side effects, including the following general statement: "Not all side effects reported for this medicine are included in this leaflet. Should your general health worsen while taking this medicine, please consult your doctor, pharmacist or other health care professional for advice"
Known symptoms of over dosage and particulars of its treatments	The statement: "In the event of over dosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre"
Identification	Identification of the medicine, i.e. the description

Package insert	Patient information leaflet
	of its physical appearance as tablet, capsule, etc.
Presentation	Presentation, which includes the number, volume or mass per package unit and a description of the packaging material, e.g. bottle, blister pack, etc.
Storage instructions, including storage temperatures	Storage and disposal information, including the following general statement: "Store all medicines out of reach of children."
Reference number (where applicable) followed by the expression "Act 101/1965"	Registration number of the medicine
Name and business address of the holder of the certificate of registration / applicant	Name, business address and telephone number of the holder of the certificate of registration
Date of publication of the package insert (where applicable)	The date of publication of the patient information leaflet

3.4 Data Analysis

Each product was recorded on a separate data collection checklist using the product's allocated designation, e.g. Product A. The corresponding product labelling information was captured on the relevant checklist under the "product label" column. An evaluation of the three sections of the data collection tool was conducted and the corresponding findings were recorded on the checklist, either in the "complies" or the "non-compliant" column. Compliant status was given if the product clearly contained the applicable information. Non-compliant status was allocated if the product contained information that did not correspond with that indicated in the monograph, or if the required information was not stated at all.

In cases where the product could not clearly be given a compliant or non-compliant status, a “partially compliant” status was given, together with an explanation. The findings were captured on an Excel® spreadsheet in tabular format. This allowed for analysis of the individual product with each aspect of the requirements, as well as comparison among the various products. The data was classified and colour-coded for its degree of compliance.

The product’s immediate and outer container labels, together with its package insert, were assessed in comparison with the monograph. Compliance with the monograph was determined using the Clinical Particulars headings prescribed under the monograph template. The Pharmacological Properties section was not included as there was either very little or no information present under this section in the monograph. Each product was assessed for compliance with each heading of the corresponding monograph. Compliance was confirmed if the information in the corresponding sections of the product’s labels or package insert agreed with the monograph. Compliance with posology was determined by calculating the dosages a patient would receive if they followed the dosage instructions provided on the product labelling, and comparing this with the information contained under posology.

Compliance with the MCC’s minimum prescribed information was determined by assessing the product’s immediate and outer container labels for the presence of the required language text. Each labelling component had to include both English and another official language in order for the products to be deemed compliant. Products were deemed partially compliant if only some of the text was in both languages.

To be deemed compliant, information had to be provided under the Category, Classification and Discipline sections. If this information was absent, non-compliant status was allocated. The absence or presence of the MCC-prescribed statement, “This medicine has not been evaluated by the Medicines Control Council. This medicine is not intended to diagnose, treat, cure or prevent any disease” was noted. The absence of this statement deemed the product non-compliant.

The product’s immediate and outer labels were inspected to detect the presence of any medicinal claims. If the product alluded to having a direct healing effect, or assured safety, this would qualify as a claim.

A product’s immediate and outer labelling, and its package insert (where present), were assessed for compliance with Regulations 8 and 9 of Act 101 of 1965, by using the data collection tool to compare the product labelling with the information required by the regulations. Where no information was provided for any of the headings, non-compliant status was allocated. In order to determine compliance with Regulation 10 of Act 101 of 1965, products were examined for the presence of a patient information leaflet. Since a detailed analysis was provided in the EMA monograph section, the safety and efficacy information required by the MCC was only assessed to the point of confirming that information was provided under headings such as indications, contra-indications, dosage and warnings.

4 Results and discussion

4.1 Products

Nine stores were visited. Products were purchased on visits to four privately owned pharmacies (one of which had a health shop inside it), one health shop, two Pharmacy Chain A stores and two Pharmacy Chain B stores. Due to the diminishing presence of private pharmacies, there were fewer of these than there were chain pharmacies. Two of each chain store were selected in order to determine if there were different products available in the larger stores. The health shop visited only sold food supplements and therefore no product was purchased there.

Each store had a different approach to displaying the products selected for the study. In some stores, products from various companies were kept under the immune-enhancing product section. An example of this is Chain store A, which classified the products under “Immune Focus”. Other stores merchandised products by manufacturer, and displayed various categories of products together. Some of the products for this study were found at the checkout counter, as part of a promotion. Products were selected if they had not been present at another store, so as to gather as broad a product range as possible. A wide range of oral dosage forms was selected. These included tinctures, tablets, capsules, effervescent tablets and throat sprays. In order to obtain a broad reflection of the current status of CM product labelling, thirteen products from various stakeholders were purchased, as presented in Table 4-1.

Table 4-1 Summary of the products selected for the study.

Product	Active ingredient(s)	Dosage form	Monograph used	Information sources
Product A	*Echinacea purpurea* herba *Echinacea purpurea* root	Liquid drops	*Echinacea purpurea* (L.) Moench, herba recens *Echinacea purpurea* (L.) Moench, radix	Immediate label Outer container label Package insert
Product B	*Echinacea purpurea* herba *Echinacea purpurea* root	Tablets	*Echinacea purpurea* (L.) Moench, herba recens *Echinacea purpurea* (L.) Moench, radix	Immediate label Outer container label Package insert
Product C	*Echinacea purpurea*	Effervescent tablets	*Echinacea purpurea* (L.) Moench, radix *Echinacea purpurea* (L.) Moench, herba recens	Immediate label Outer container label Package insert
Product D	Black elderberry extract (*Sambucus nigra*)	Tablets	*Sambucus nigra* L., Flos	Immediate label Package insert
Product E	*Pelargonium sidoides* root	Liquid: throat spray	*Pelargonium sidoides* DC	Immediate label Outer container label Package insert
Product F	*Pelargonium sidoides*	Effervescent tablets	*Pelargonium sidoides* DC	Immediate label Outer container label Package insert
Product G	*Pelargonium sidoides* root *Sambucus nigra*	Tablets	*Pelargonium sidoides* DC *Sambucus nigra* L., Flos	Immediate label Outer container label Package insert Patient Information Leaflet
Product H	*Sambucus nigra*	Capsules	*Sambucus nigra* L., Flos	Immediate label Outer container label

Product	Active ingredient(s)	Dosage form	Monograph used	Information sources
Product I	*Sambucus nigra* *Pelargonium sidoides*	Liquid: throat spray	*Pelargonium sidoides* DC *Sambucus nigra* L., Flos	Immediate label Outer container label Package insert
Product J	*Echinacea* extract Elderberry extract (*Sambucus nigra*)	Tablets	*Echinacea angustifolia* DC., radix *Echinacea purpurea* (L.) Moench, radix *Echinacea purpurea* (L.) Moench, herba recens *Sambucus nigra* L., Flos	Immediate label Outer container label Package insert
Product K	*Echinacea* extract Elderberry (*Sambucus nigra*)	Capsules	*Echinacea angustifolia* DC., radix *Echinacea purpurea* (L.) Moench, radix *Echinacea purpurea* (L.) Moench, herba recens *Sambucus nigra* L., Flos	Immediate label
Product L	*Echinacea purpurea*	Effervescent tablets	*Echinacea purpurea* (L.) Moench, radix *Echinacea purpurea* (L.) Moench, herba recens	Immediate label Outer container label Package insert
Product M	*Echinacea*	Capsules	*Echinacea angustifolia* DC., radix *Echinacea purpurea* (L.) Moench, radix *Echinacea purpurea* (L.) Moench, herba recens	Immediate label Outer container label Package insert

Where product labelling was non-specific as to which herbal plant part or species was present in the formulation (such as *Echinacea*, which may be a *Purpurea* or *Angustifolia*), all available monographs were used for comparison. This was done to broaden the study, by checking that if one area appeared non-compliant, it could be compliant with another monograph. The labelling on some of the products containing *Echinacea* did not indicate whether the *Echinacea* radix (root) or herba recens (fresh herbal extract) was used.

The *Echinacea purpurea* monograph for the herba recens contains both the well-established use and the traditional use. The well-established use was selected as it contains the indication for the common cold, while the traditional use was cutaneous, for treating dermal wounds. Some of the products also contained vitamins and minerals, or other herbal ingredients which were potentially related to another CM discipline. Only the herbal ingredients that had a corresponding monograph were included in the study.

4.2 European Medicines Agency Herbal Monographs

The monographs were located on the EMA website. One was located for *Sambucus nigra* and another for *Pelargonium sidoides*. Three monographs were found for *Echinacea*, namely *Echinacea purpurea* radix, *Echinacea purpurea* herba recens and *Echinacea angustifolia*.

4.2.1 Qualitative and Quantitative Composition

The monographs are specific as to what the composition for each herbal ingredient should be. The composition is required to be either a herbal substance or a herbal preparation. The herbal preparation category is further divided into herbal substances, tinctures, and dry or liquid extracts. The labelling of the various products was assessed and as far as possible compliance with the required composition was determined. None of the products were deemed fully compliant with the qualitative and quantitative composition stipulated by the corresponding monograph.

Product E provided conflicting information on the immediate container label (136,25 mg/ml), outer container label (138 mg/ml), and the package insert (234 mg) regarding the active ingredient composition quantity. The quantity value of 138mg/ml was chosen for the posology assessment in Table 4-5.

Further insight into the quality and manufacturing processes is required to verify the herbal ingredient composition. However, the results from this section of the study highlight that quality aspects (such as information about the active herbal ingredients) are not verified, and therefore the safety and efficacy of the CM is not substantiated.

4.2.2 Pharmaceutical Form

Most of the products (85 %) appeared to comply with the corresponding monograph's pharmaceutical forms. This percentage of compliance was determined by excluding the *Sambucus nigra* component in the combination products, as this should be in liquid

form, and excluding two of the products for which compliance could not be determined. The solid dosage form products containing *Sambucus nigra* did not comply as this is supposed to be in the form of either a herbal tea or an oral liquid. An exception to this was Product H, whose compliance could not be fully determined as it was stated to be equivalent to fresh juice.

Kinoshita *et al.* (2012, p.1637) noted that their study on *Sambucus nigra* demonstrated a stronger *in vivo* than *in vitro* effect against the Human Influenza A virus. This was dissimilar to results from other studies. The authors propose that this may be because they used the concentrated juice of elderberry, while other researchers may have used commercial preparations for which the exact extraction methods were not known (Kinoshita *et al*, 2012, p.1637) therefore, the pharmaceutical form has a direct influence on efficacy.

The effect of pharmaceutical form is further emphasised in a study by Roxas and Jurenka (2007, p. 40), where it was proposed that the varied conclusions into *Echinacea*'s efficacy may result from the part of the plant studied, as well as the extraction process used. It is therefore imperative that manufacturers and regulators ensure the correct form is used.

4.2.3 Therapeutic Indications

All the products contained more indications than the monographs, and were therefore only partially compliant. The majority of the products were indicated for the treatment of

colds and flu, while their corresponding monographs indicated the treatment of colds only.

4.2.3.1 Products Containing Echinacea

According to the therapeutic indications of the monograph, *Echinacea purpurea* radix (EMA, 2010) and *Echinacea angustifolia* radix (EMA, 2012a) are indicated for supportive treatment of the common cold. *Echinacea purpurea* herba recens (EMA, 2014a) is indicated for the short-term prevention and treatment of the common cold. Table 4-2 summarises the therapeutic indications on the medication label, compared with the indications listed in the monograph.

Table 4-2 Therapeutic indications on the label for products containing *Echinacea*, compared with European Medicines Agency monograph (compliant indications in normal text and non-compliant indications in bold).

Product	**Indications on medication label and/or package insert (PI)**
Product A	Immediate container label: "A herbal remedy recommended for the **prevention and** treatment of: colds, **influenza type infections and similar upper respiratory tract conditions, sore throat, recurring winter ills and lower urinary tract infections. Assists to modulate the immune response to infections."** Outer container label and package insert: "A herbal remedy with supportive therapy for the **prevention and** treatment of colds, **influenza type infections and similar upper respiratory tract conditions, sore throats and mild lower urinary tract infections. Assists to modulate the immune response to infections.**"
Product B	
Product C	Label "**Immune booster"** **"Echinacea's action is primarily directed toward the immune system. This herb has demonstrated antibacterial, anti-inflammatory, antiseptic and immune system enhancing properties."**
Product J	Claim specific to *Echinacea*:

	"Assists to maintain and support the immune system."
Product K	"Assists in the **prevention** and relief of Cold **and Flu symptoms."**
Product L	PI *Echinacea purpurea* ext.: "Herbal extract with a **stimulant effect on the immune system**, increasing the body's natural resistance to infections, especially colds **and flu**."
Product M	PI *Echinacea*: "Aids in the treatment and prevention of colds **and flu and related infections.** **Exerts an immune stimulatory and anti-inflammatory effect to reduce the severity and duration of the symptoms commonly associated with colds and flu."**

These products were assessed to be non-compliant because of indications not stated in the monograph, such as the indication for the prevention of colds and flu. However, Jawad *et al.* (2012, p.2) conducted a clinical trial in human subjects using Echinaforce® Drops (a product containing *Echinacea*) as a four-month therapy to determine if it had a prophylactic effect against the common cold. The study group who received these drops had a smaller incidence of experiencing a common cold episode. This may support the indication for cold prevention, and it was concluded that the long-term use (four months) of Echinaforce® Drops could be supported (Jawad *et al*., 2012, p.6).

In a pre-clinical study by Hudson and Vimalanathan (2011, p.1025) it was determined that Echinaforce® Drops showed activity against viruses with membranes. These viruses included Influenza A and B (Hudson and Vimalanathan, 2011, p.1025). These findings may support indications for influenza-type infections. Another pre-clinical study by Fusco *et al*. (2010, p.2) used mice infected with influenza and investigated the effects of *Echinacea purpurea* herbal extract. The study showed that influenza-infected mice administered with the *Echinacea* showed better clinical outcomes than those

which were not (Fusco *et al*., 2010, p.4). The indications for influenza may therefore be supported. However, further clinical research is required.

4.2.3.2 Products Containing Sambucus

The monograph for *Sambucus nigra* indicates its use in the relief of early symptoms of the common cold (EMA, 2008). Table 4-3 summarises the therapeutic indications on the medication labels of products containing *Sambucus*, as compared to the monograph.

Table 4-3 Therapeutic indications on the label for products containing *Sambucus*, as compared to the European Medicines Agency monograph (compliant indications in normal text and non-compliant indications in bold).

Product	**Indications on medication label and/or package insert (PI)**
Product D	**"Contributes to a healthy immune system."** PI: **"Assists in supporting the function of the immune system and** may help to soothe the minor symptoms associated with colds **and flu**."
Product G	"For the symptomatic relief of colds **and flu**."
Product H	"Cold **and Flu** **Congestion** **Cough** **Aches & Pains** **Fever** **Sore throat"**
Product I	"Soothes and protects against cold **and flu** symptoms"
Product J	"Assists to reduce cold and **flu** symptoms due to its **anti-congestion properties"**
Product K	"Assists in the **prevention** and relief of Cold **and Flu symptoms."**

The products containing *Sambucus nigra* complied with the monograph indications pertaining to colds. However, these products were deemed non-compliant with respect to the additional indications related to flu. Roxas and Jurenka (2007, p.40) describe that two randomised, double-blind, placebo-controlled studies using the product Sambucol™ (which contains *Sambucus*) supported the indication for flu. In these studies Sambucol™ showed activity against Influenza A and B. Zakay-Rones *et al*. (2004, p.137) explain that *Sambucus* could be effective in the treatment of flu, as it has been shown that *Sambucus* can inhibit the adhesion of the influenza virus to body cell receptors.

4.2.3.3 Products Containing Pelargonium

The monograph for *Pelargonium sidoides* indicates its use in the symptomatic treatment of the common cold (EMA, 2012b). Table 4-4 summarises the therapeutic indications on the labels of products containing *Pelargonium*, as compared to the monograph.

Table 4-4 Therapeutic indications on the label for products containing *Pelargonium,* as compared to the European Medicines Agency monograph (compliant indications in normal text and non-compliant indications in bold).

Product	Indications on medication label and/or package insert (PI)
Product E	**"Infection support associated with** colds **and flu."** "*Pelargonium sidoides* can assist the body with **immune support** and to relieve symptoms associated with the common cold **as well as acute and chronic respiratory infections."** **"Can assist the body with:** **Anti-viral support** **Anti-bacterial support** **Infection support associated with colds and flu** **Immune support** **Symptomatic relief"**

Product F	Label: "Infection support associated with colds **and flu. Hay fever support"** PI**: "*Pelargonium sidoides* can assist the body with symptomatic relief associated with respiratory tract infections. The active ingredients can also provide hay fever support."**
Product G	"For the symptomatic relief of colds **and flu.**"
Product I	"Soothes and protects against cold **and flu** symptoms."

The products containing *Pelargonium* all followed the same trend in that they were compliant in their indications for the common cold, but were non-compliant in their indications for flu.

4.2.4 Posology

Every product was found to be non-compliant when compared with the posology required by its corresponding monograph (Table 4-5). A trend identified across six of the products was that they contained the dosage and directions for use for children, where the corresponding monograph did not recommend the use in children under 12 years old.

Table 4-5 Summary of comparison between dosage and maximum daily dosage between the medication label and/or package insert, and the European Medicines Agency monograph.

		Medication label and/or package insert		**EMA monograph**	
Product	**Active ingredient**	**Strength/quantity per dosage form**	**Maximum recommended daily dosage**	**Recommended daily dosage**	**Conclusion**
Product A	*Echinacea purpurea*	614 mg/ml		*E. purpurea* herba recens*	N/A

		Medication label and/or package insert		EMA monograph	
Product	**Active ingredient**	**Strength/quantity per dosage form**	**Maximum recommended daily dosage**	**Recommended daily dosage**	**Conclusion**
	Herba				
	Echinacea purpurea Root / radix	32 mg/ml	160 mg	360 mg	Underdose
Product B	*Echinacea purpurea* Herba	1 140 mg per tablet		*E. purpurea* herba recens*	N/A
	Echinacea purpurea Radix	60 mg per tablet	180 mg	360 mg	Underdose
Product C	*Echinacea purpurea*	50 mg per tablet	50 mg	*E. purpurea* radix: 360 mg *E. purpurea* herba recens*	Underdose N/A
Product D	Black elderberry extract (*Sambucus nigra*)	50 mg per tablet	200 mg	*Sambucus nigra* 15 000 mgł	Underdose
Product E	*Pelargonium sidoides* root	138 mg/ml**	6 624 mg	*Pelargonium sidoides* 60 mg	Overdose
Product F	*Pelargonium sidoides*	350 mg per tablet	1 050 mg	60 mg	Overdose
Product G	*Pelargonium sidoides* root	20 mg per tablet	20 mg	*Pelargonium sidoides* 60 mg	Underdose
	Sambucus nigra	20 mg per tablet	20 mg	*Sambucus nigra* 15 000 mgł	Underdose
Product H	*Sambucus nigra*	3 800 mg per capsule	22 000 mg	*Sambucus nigra* 15 000 mgł	Overdose
Product I	Elderberry extract	250 mg/ml	9 g	*Sambucus nigra* 15 000 mgł	Within the range of

		Medication label and/or package insert		EMA monograph	
Product	**Active ingredient**	**Strength/quantity per dosage form**	**Maximum recommended daily dosage**	**Recommended daily dosage**	**Conclusion**
	(*Sambucus nigra*)				6-15 g per day
	Pelargonium extract (*Pelargonium sidoides* 12,5%)	136 mg/ml	4 896 mg	*Pelargonium sidoides* 60 mg	Overdose
Product J	*Echinacea* extract	80 mg per tablet	240 mg	*E. angustifolia* 1 500 mg *E. purpurea* radix 360 mg *E. purpurea* herba recens*	Underdose Underdose N/A
	Elderberry extract (*Sambucus nigra)*	20 mg per tablet	60 mg	*Sambucus nigra* 15 000 mgł	Underdose
Product K	*Echinacea* extract	100 mg per capsule	800 mg	*E. angustifolia* 1 500 mg *E. purpurea* radix 360 mg *E. purpurea* herba recens *	Underdose Overdose N/A
	Elderberry (*Sambucus nigra)*	100 mg per capsule	800 mg	*Sambucus nigra* 15 000mgł	Underdose
Product L	*Echinacea purpurea*	240 mg per tablet	240 mg	*E. purpurea* radix 360 mg *E. purpurea* herba recens*	Underdose

		Medication label and/or package insert		EMA monograph	
Product	**Active ingredient**	**Strength/quantity per dosage form**	**Maximum recommended daily dosage**	**Recommended daily dosage**	**Conclusion**
Product M	*Echinacea*	75 mg per capsule	225 mg	*E. angustifolia* 1 500 mg *E. purpurea* radix 360 mg *E. purpurea* herba recens*	Underdose Underdose N/A

Key:

* *Echinacea purpurea* herba recens: Dose compliance could not be determined, as the monograph provides the posology in terms of expressed juice.

** Strength as provided on the outer container label (conflicting data was present on the labelling components).

ł *Sambucus nigra*: Based on the posology for the herbal substance for tea preparation.

4.2.5 Duration of Use

The monographs for each herbal substance stipulate for how long the product should be used, and whether medical attention is required after a stipulated amount of time. All the products were non-compliant in that the duration of use was not stated. This poses a risk that patients may continue to use products without symptom improvement and neglect to seek medical assistance.

4.2.6 Contra-indications, Special Warnings and Precautions for Use

All the products, with the exception of two, complied with the corresponding monograph contra-indications. Two products were deemed non-compliant as they did not provide any contra-indications. Only one product fully complied with the special warnings and precautions for use. Products were seen to partially comply if their labelling contained some of the information contained under the heading.

The warnings and special precautions in the *Pelargonium sidoides* monograph included those related to hepatotoxicity (EMA, 2012b). Two of the products were non-compliant, as none of their warnings correlated to those in the EMA monograph. However, both contained warnings related to the blood-thinning effect of *Pelargonium* and carried a warning regarding interactions with warfarin or other such medications. Patrick and Hickner (2008, p.160) describe that *Pelargonium* contains plant coumarins, and that in theory there are possible medicine interactions with anti-coagulants. However, the authors state that there have not been any serious adverse events related to bleeding (Patrick and Hickner, 2008, p.160). In a study by Brendler and van Wyk (2008, p.429), the authors affirmed that the coumarins identified in the study's extract of *Pelargonium* did not appear to exert anti-coagulant effects.

4.2.7 Pregnancy and Lactation

All the monographs, except one, contained a statement that the use of the herbal product was not recommended during pregnancy, as there was not enough relevant safety data. The exception was the monograph for *Echinacea purpurea* herba recens,

which stated that while some data was available, a doctor should be consulted before use during pregnancy (EMA, 2014a).

Only two products complied with their corresponding monographs. The remainder of the products were non-compliant for various reasons. Non-compliance was determined for products containing labelling which stated that no side effects had been recorded, instead of stating that there was a lack of data. This could mislead a patient into thinking that the product is safe. Non-compliance was allocated for products containing statements that allowed for consultation with a healthcare practitioner, as this carries the risk that an insufficiently informed person may be consulted. Non-compliance was allocated for products which only stated that use in pregnancy and lactation has not been established, rather than stating that it is not recommended.

4.2.8 Effects on Ability to Drive and Use Machines

All five product monographs stated that no studies had been conducted in this area. Although one product provided information in this category, it did not comply. It stated that it was safe to drive during product use. This was untrue as the specific monograph stated that there was no data available.

4.2.9 Undesirable Effects

The undesirable effects for the three monographs for *Echinacea* ranged from dermal to severe hypersensitivity reactions. Products A, B, C and L partially complied in that they listed hypersensitivity reactions but did not specify all the reactions listed in the

monographs. Product M was non-compliant as it only listed gastrointestinal disturbances, which did not appear in the monographs.

The monograph for *Sambucus nigra* describes that there are no known undesirable effects, but that if any adverse reactions occur, medical consultation is to be sought (EMA, 2008). Product D partially complied as it stated there were no known side effects, but it did not advise seeking medical advice.

Some of the undesirable effects listed in the *Pelargonium sidoides* monograph included gastrointestinal effects, nasal bleeding, allergic reactions and hepatotoxicity (EMA, 2012b). Product E partially complied in that it carried the advice that medical attention should be sought if any side effects were experienced. Product F carried the same advice, but was non-compliant as it further stated that there were no reported side effects. However, both products contained symptoms in the overdosage section that were similar to those listed in the monograph's undesirable effects.

Products G and I stated that there were no known side effects, which made them non-compliant with the *Pelargonium* requirements, and compliant with the *Sambucus* requirements. Similarly, Product J did not comply as it stated that there were no known side effects, which is not true for the *Echinacea* ingredients. Products H and K were non-compliant as they did not state any side effects.

4.2.10 Overdose

All the monographs stated that there were no reported overdose cases. The products were compliant if relevant safety information was provided under this section, such as

advice to seek medical assistance in the event of an overdose. Six of the products did not contain any information and were deemed non-compliant.

4.3 Compliance with MCC Requirements

This was determined by investigating whether the product fully complied with the requirements or did not comply at all. Partial compliance with the requirement to provide text in one other official language was allocated for products that contained only part of the text in another language. Partial compliance was also allocated in instances where the required phrase pertaining to medical assistance was provided, but was not identical to the MCC's wording.

Table 4-6 Summary of number of products (n=13) complying with Medicines Control Council (MCC) minimum criteria and actual medication label.

MCC minimum criteria	Number of products complying	Number of products partially complying	Number of products non-compliant
Written in English and at least one other official language	2	1	10
Category of medicine	1	0	12
Pharmacological classification of the medicine	1	0	12
Discipline of medicine	1	0	12
The words: "This medicine has not been evaluated by the Medicines Control Council. This medicine is not	6	0	7

MCC minimum criteria	Number of products complying	Number of products partially complying	Number of products non-compliant
intended to diagnose, treat, cure or prevent any disease."			
All claims relating to symptoms must be accompanied by the advice: "If symptoms persist consult your healthcare practitioner."	4	3	6
No medicinal claims: Immediate label	11	0	2
Carton	13	0	0
Package insert	13	0	0

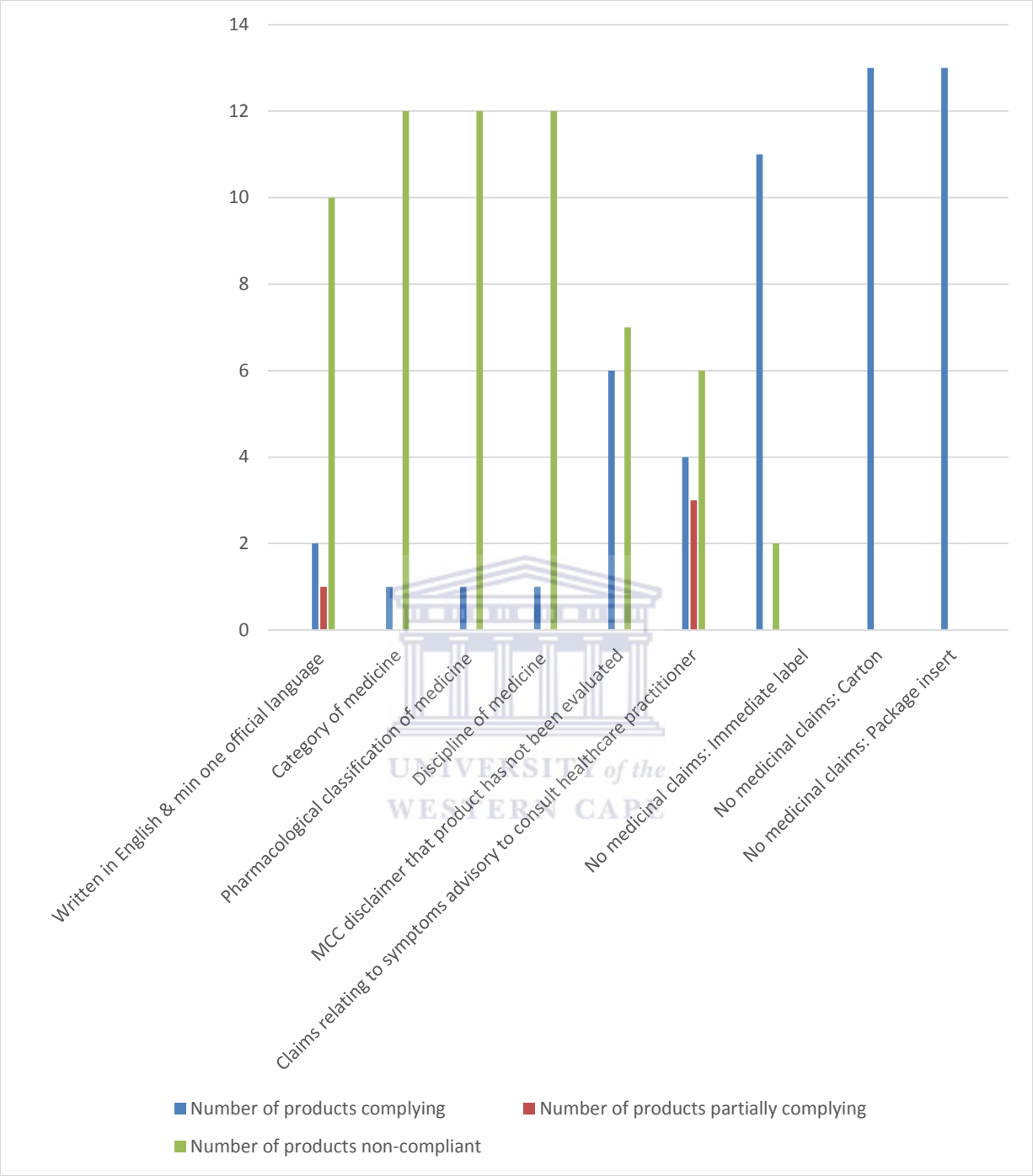

Figure 4-1 Graph illustrating number of products (n=13) complying with Medicines Control Council (MCC) minimum criteria and actual medication label.

The category of medicine and the pharmacological classification were provided on the immediate and outer labels of product G only. For the other products this information

was provided only in the package insert. Product G was also the only product to provide the discipline of the medicine on its label.

Eleven of the products did not contain direct medicinal claims, as phrases such as “soothes”, “assists” and “supports” were present. However, Products A and B provided conflicting information on the immediate container label and the outer container label, as reflected in Table 4-2. Since the immediate container label did not contain the term “supportive” and merely stated “recommended”, this could be interpreted as a medicinal claim. The immediate container label was deemed non-compliant.

4.4 Labelling Requirements in Terms of Act 101 of 1965

4.4.1 Regulation 8: Information on Immediate and Outer Container Labels

Table 4-7 Information on immediate and outer container labels as required by regulation 8 of Act 101 of 1965.

Immediate label n = 13
Outer label n = 11

Requirements	Immediate container label			Outer container label		
	Number of products compliant	Number of products partially compliant	Number of products non-compliant	Number of products compliant	Number of products partially compliant	Number of products non-compliant
Scheduling status (where applicable)	1	0	12	1	0	10
Proprietary name of the medicine	13	0	0	11	0	0
Registration/reference number	1	0	12	1	0	10

Requirements	Immediate container label			Outer container label		
	Number of products compliant	**Number of products partially compliant**	**Number of products non-compliant**	**Number of products compliant**	**Number of products partially compliant**	**Number of products non-compliant**
Dosage form	12	0	1	11	0	0
Approved name of each active ingredient of the medicine	13	0	0	11	0	0
Quantity thereof contained in a dosage unit, or per suitable mass or volume or unit	11	0	2	10	0	1
Content of the medicine package expressed in the appropriate unit or volume of the medicine	11	0	2	11	0	0
Lot number	13	0	0	11	0	0
Expiry date	13	0	0	11	0	0
Name of the holder of certificate of registration (or name of applicant)	12	0	1	11	0	0
Storage temperature and other precautions required for the preservation of the medicine	12	0	1	11	0	0
The warning: “Keep out of reach of children”	12	0	1	11	0	0

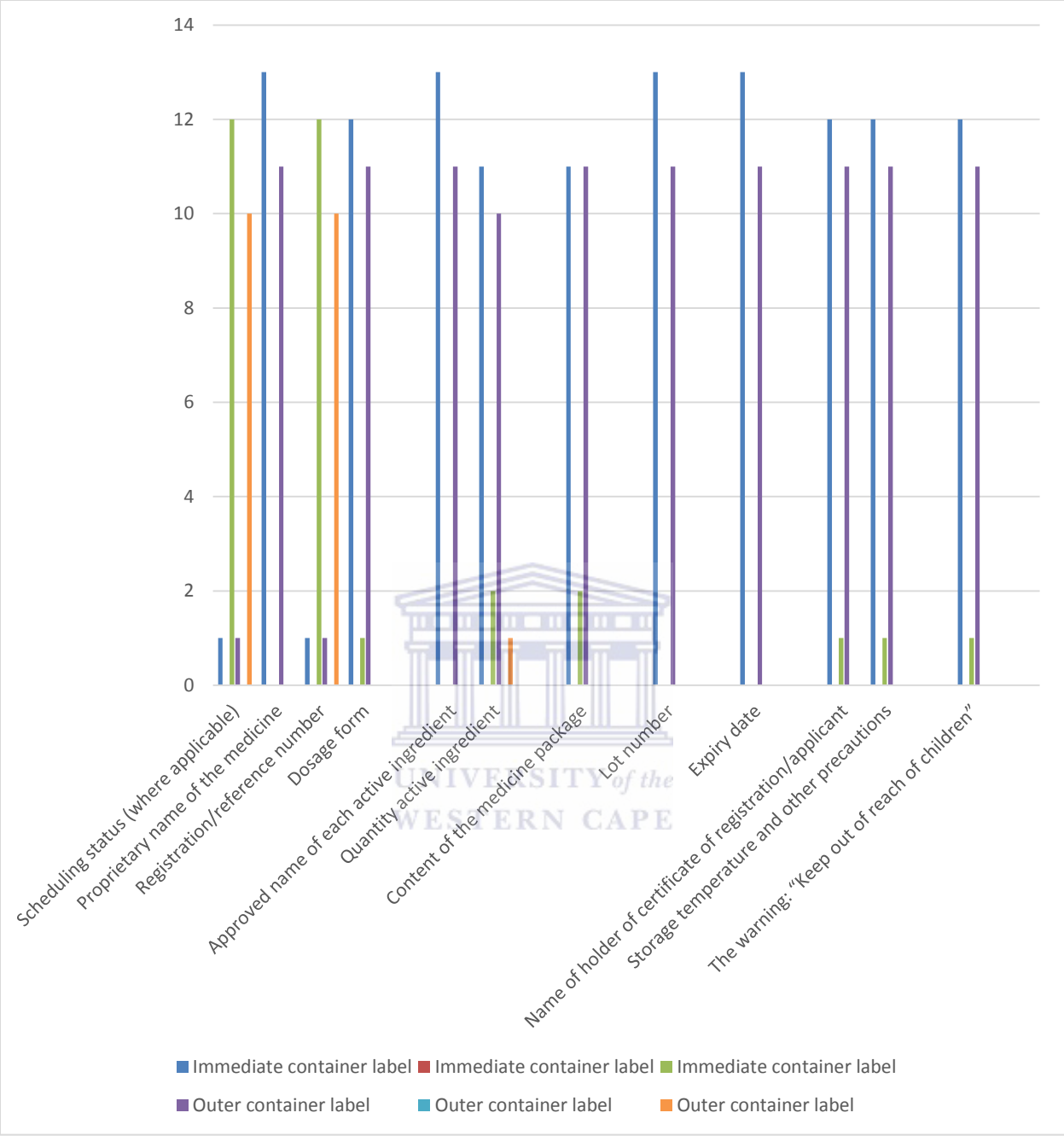

Figure 4-2 Graph illustrating compliance with Information on immediate and outer container labels as required by regulation 8 of Act 101 of 1965.

All the products contained a label affixed to the immediate container, featuring text in English. Eleven of the products featured an outer container label. Only one product, Product G, contained a scheduling status (S 0). While medicines in this category of CMs are not scheduled, there should still be information in the package insert stating that the product is unscheduled, or S 0.

Only two of the products contained information pertaining to the preservative content. Product I stated that it contained no preservatives, and only the outer container label of Product E stated that alcohol was the preservative. Product E was the only product stating sugar content, and while Product G stated that it contained sugar, it did not provide the quantity thereof. Products A and E provided alcohol content information. None of the products contained a tartrazine warning. Since the product formulations were not evaluated in this study, it cannot be determined if the products required this warning.

The products were assessed to determine whether the indications were provided. The accuracy of the indications has been discussed in 4.2.3 (Therapeutic Indications). Products C and H did not contain any indications on their immediate labels, but both contained the indications on the outer label. Similarly, dosage was only assessed for presence, not accuracy. The immediate labels of products H and I were non-compliant, as the only dosage instruction was to refer to the package insert. However, the outer labels of these two products provided the dosage instructions.

One product contained a “Reg. No.” on its immediate and outer container label, while this was deemed compliant in that a number was provided, the terminology “Reg. No.”

which was used is not correct. No CMs have yet been evaluated by the MCC, and therefore referring to the number provided as a registration number implies that the product has undergone evaluation and is approved. The more appropriate term is “complementary registry number”, as seen in the package inserts of some of the products. It is most likely that the number referenced is not a registration number, but a registry number, provided by the MCC during the call up in 2002. This is confirmed by the product’s package insert, whereby the “registration number” contained a statement that the registration number was “to be allocated”.

4.4.2 Regulation 9: Information on Package Inserts

Two of the products did not contain package inserts, and therefore were deemed non-compliant with all the package insert requirements. Subsequent analysis refers only to the products that contained package inserts. For a summary of the information present in the package inserts, refer to Table 4-8.

One product provided a “product information leaflet” containing similar information to that required by the package insert, but the information was not provided in the format of the package insert requirements. All the package inserts were in English, and nine were in Afrikaans as well.

Compliance with the scheduling status requirement was fulfilled if information was listed either as S 0, “not scheduled”, or “not applicable”. One product was deemed partially compliant as it stated “nutritional supplement” under the scheduling status.

Compliance was granted for the reference number requirement if relevant information was provided, such as the number, or the phrases “to be allocated” or “pending”. Two products contained postal address information instead of the physical address, and were deemed non-compliant.

Table 4-8 Information appearing on the package insert of products (n=11) as compared to the requirements as stipulated in Act 101 of 1965.

Required information	Number of products compliant	Number of products partially compliant	Number of products non-compliant
Scheduling status (where applicable)	7	1	3
Proprietary name and dosage form	11	0	0
The approved name of each active ingredient	11	0	0
Quantity thereof contained in a dosage unit or per suitable mass or volume or unit of the medicine	10	1	0
Identification	11	0	0
Presentation	11	0	0
Storage instructions, including storage temperatures	7	4	0
Reference number (where applicable) followed by the expression: "Act 101/1965"	9	0	2

Required information	Number of products compliant	Number of products partially compliant	Number of products non-compliant
Name and business address of the holder of the certificate of registration/applicant	9	0	2
Date of publication of the package insert (where applicable)	10	0	1

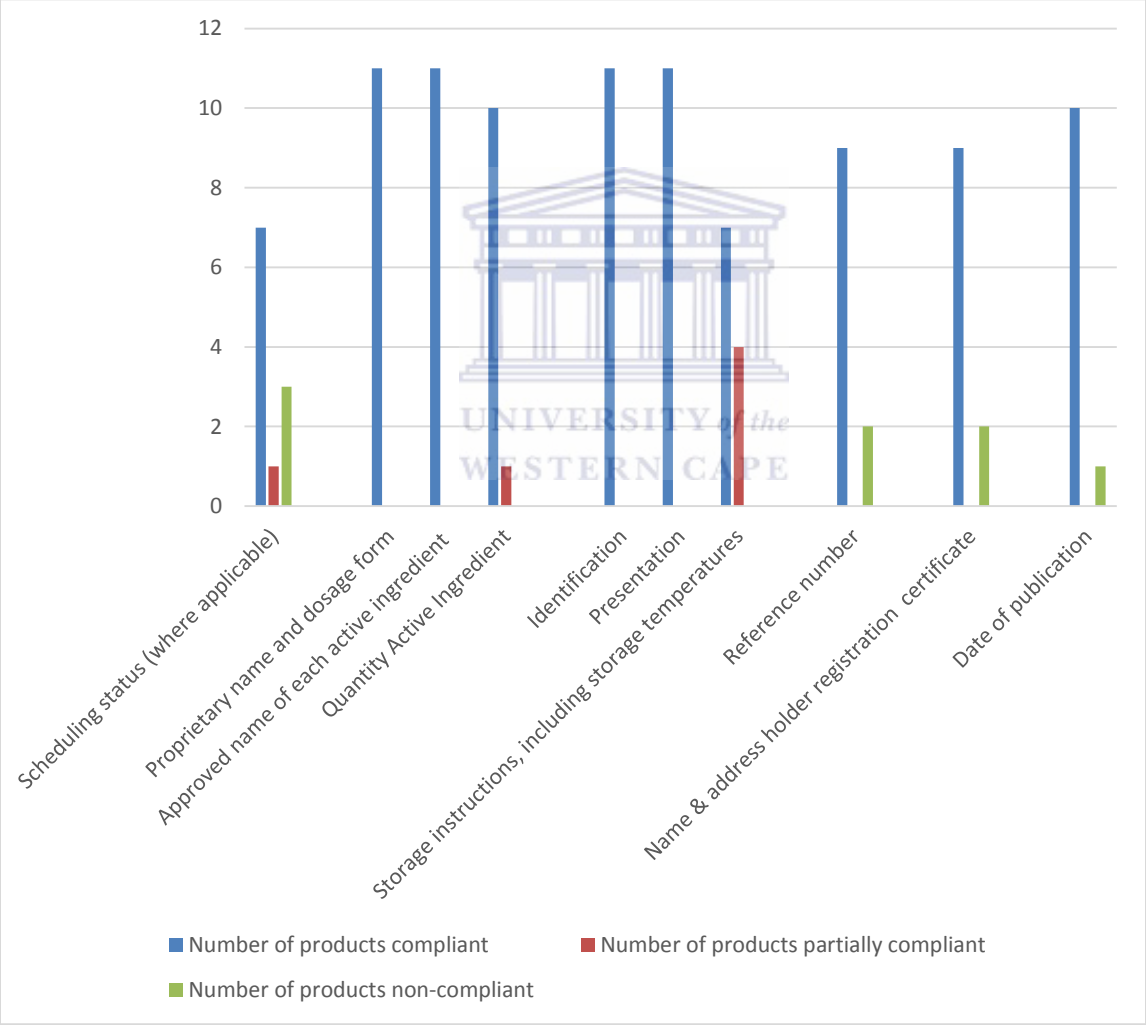

Figure 4-3 Graph illustrating compliance of information appearing on the package insert of products (n=11) as compared to the requirements as stipulated in Act 101 of 1965.

Only product E provided information about preservative content. Compliance or non-compliance regarding preservative information could not be determined in the other products, as it was not known if their formulation included preservatives. It is likely that they would contain preservatives, however, in which case they would be non-compliant. Two of the liquid formulations provided information about their alcohol content, and were therefore compliant. Products C, G and M contained information pertaining to sugar.

Nine of the products were deemed compliant for containing a reference number, in that they either contained the statement “to be allocated” or the provided number was preceded by: “complementary registry number”. This demonstrated that the numbers were not medicine registration numbers, and that the products had not been evaluated.

4.4.2.1 Pharmacological Classification and Pharmacological Action

The MCC has classified immune boosters under: 32.16 (Other) Immune Boosters (MCC, 2013b). Various classifications appeared in the package inserts. The results for this section are depicted in Figure 4-1 (presented overleaf).

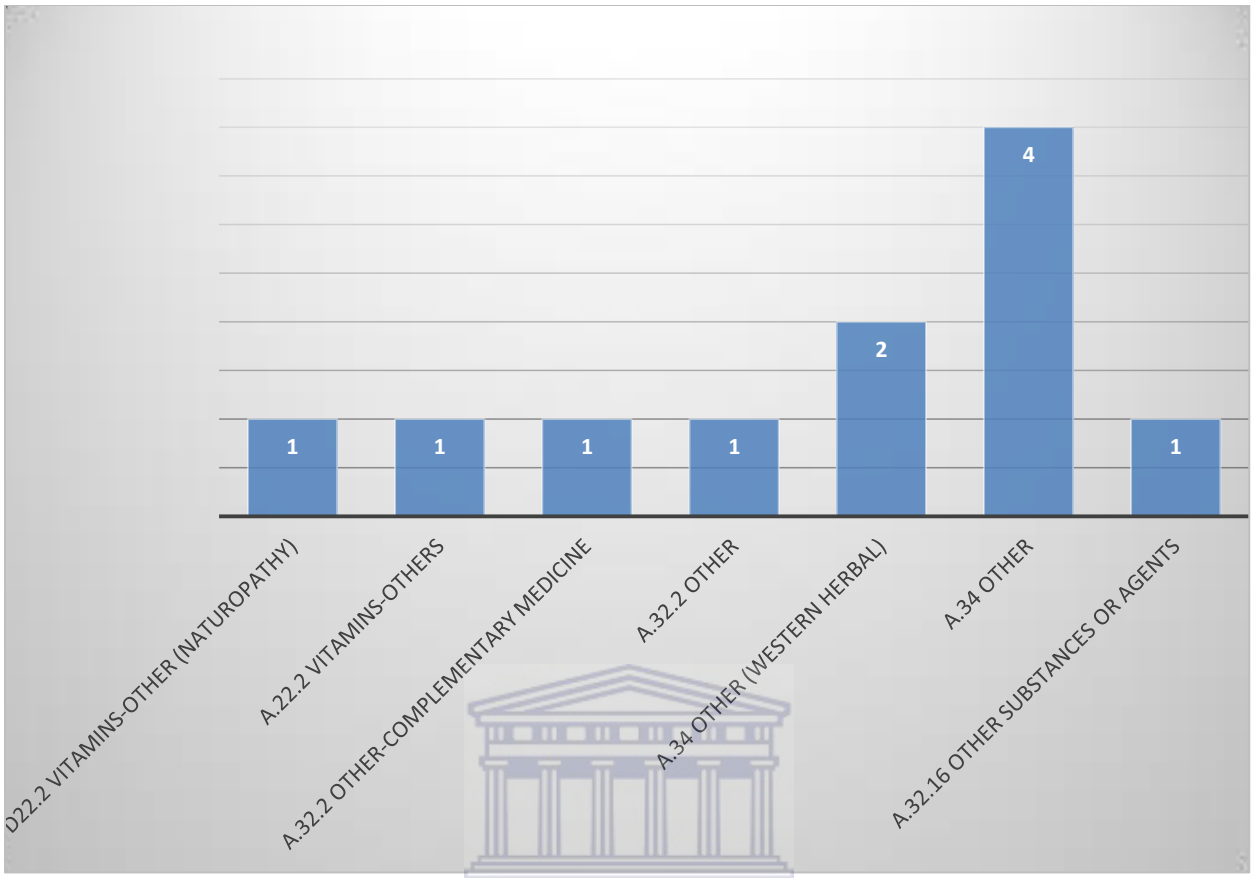

Figure 4-4 Pharmacological classification as per the package insert of the sampled products (n=11).

Category D.22.2 Vitamins-Other (Naturopathy) is not correct. Even though the product contained vitamins, its Western Herbal discipline is not recognised. Category A.22.2 is likely to be outdated as CMs now fall under Category D. Similarly, Category A 32.2-Other would be outdated, even in the case where the manufacturer has stated that it is a complementary medicine. Four of the products were classified under category A. 34, but this category was not found in the Regulations of Act 101 of 1965. These results demonstrate that there is uncertainty as to which classification should be used. Nine of the products contained information under the pharmacological action heading.

4.4.2.2 Sections Corresponding to the European Medicines Agency Monographs

The sections presented in Table 4-9 were assessed to determine if information was provided under the required headings of Regulation 9 of Act 101 of 1965. Products were deemed compliant if the information was in accordance with the information presented in the monographs. Products were deemed partially compliant if information was provided in the package insert, but was not consistent with the monographs. Products were deemed non-compliant if no information was provided.

Table 4-9 Compliance with Regulation 9 sections corresponding to European Medicines Agency (EMA) monograph (n=11).

Heading	Product										
	A	B	C	D	E	F	G	I	J	L	M
Indications	+	+	+	+	+	+	+	+	+	+	+
Contra-indications	=	=	+	+	=	=	+	=	+	=	=
Warnings	=	=	=	=	=	=	+	=	-	=	=
Interactions	=	=	=	=	+	+	=	-	-	-	=
Pregnancy	+	+	+	+	+	+	+	+	-	+	=
Dosage and directions for use	+	+	+	+	+	+	+	+	+	+	+
Side effects and special precautions	+	+	=	=	=	=	=	=	=	+	=
Known symptoms of overdosage and particulars	+	+	+	+	+	+	+	+	+	+	+

Heading	Product										
	A	B	C	D	E	F	G	I	J	L	M
of its treatments											

Key:

+ Complies in that information was provided

= Complies with EMA monograph

- Non-compliant

4.4.3 Regulation 10: Information on Patient Information Leaflets

Only product G contained a patient information leaflet. As there was only one patient information leaflet available for the study, no further analysis was conducted into compliance in this regard.

4.5 Limitations of the Study

The majority of the products did not conform to the EMA monographs. A limitation of this study is that only EMA monographs were used to assess compliance, and perhaps the use of other monographs recognised by the MCC would provide additional information surrounding compliance. However, the EMA remains a reputable and MCC-recognised reference source.

Another limitation is that the labelling of the products in this study may have been superseded with conformant labelling by the time of this writing. CM companies may have revised and updated product labelling in order to comply with the MCC's guidelines, and these new batches of products could now be available on the market.

4.6 Overall Compliance

An overall percentage compliance for each product was allocated to each of the three sections of the data collection tool. This was determined by assigning each variable a level of compliance as follows: 0 for non-compliance; 0,5 for partial compliance or where information only complied in that it was provided; and 1 for total compliance. In order to determine the percentage of compliance, the total value was added up and divided by the number of headings. Appendix 3 details the variables included and excluded in the assessment. The overall compliance of each product with each section of the data assessment is demonstrated below, in Figures 4-2 to 4-4.

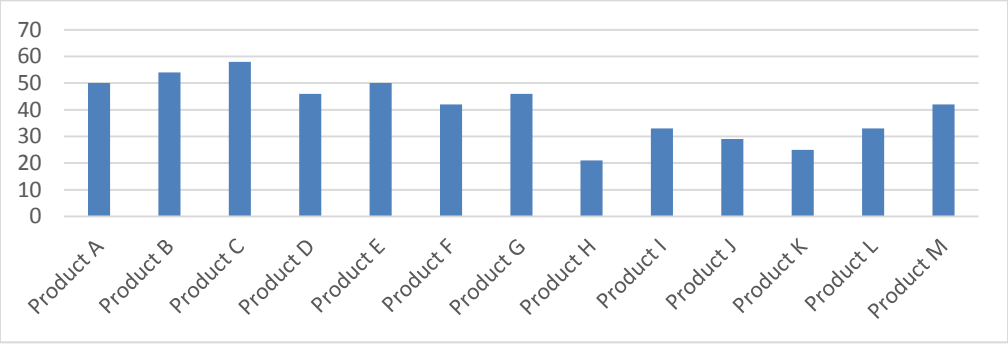

Figure 4-5 Percentage compliance of each product with the European Medicines Agency monograph.

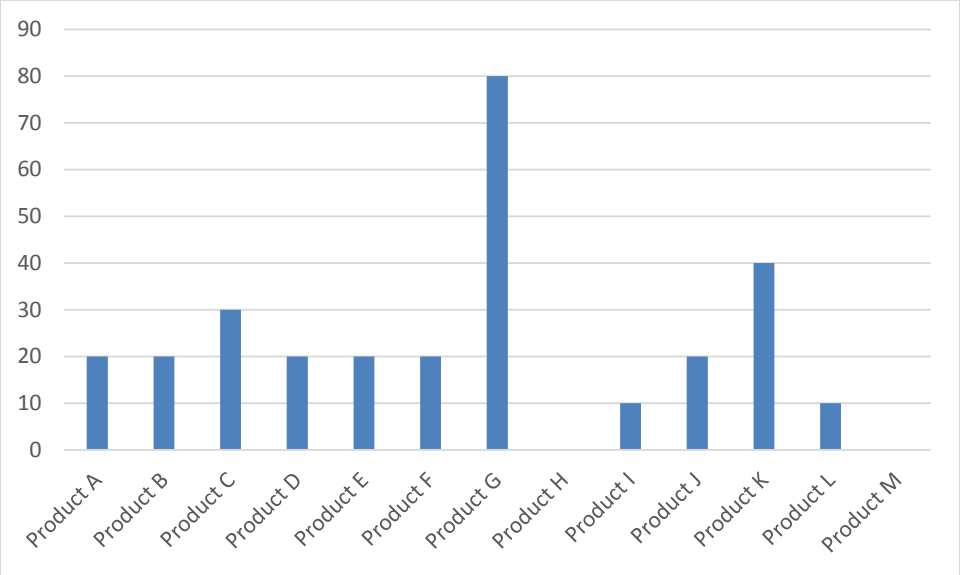

Figure 4-6 Percentage compliance of each product with the Medicine Control Council's minimum requirements.

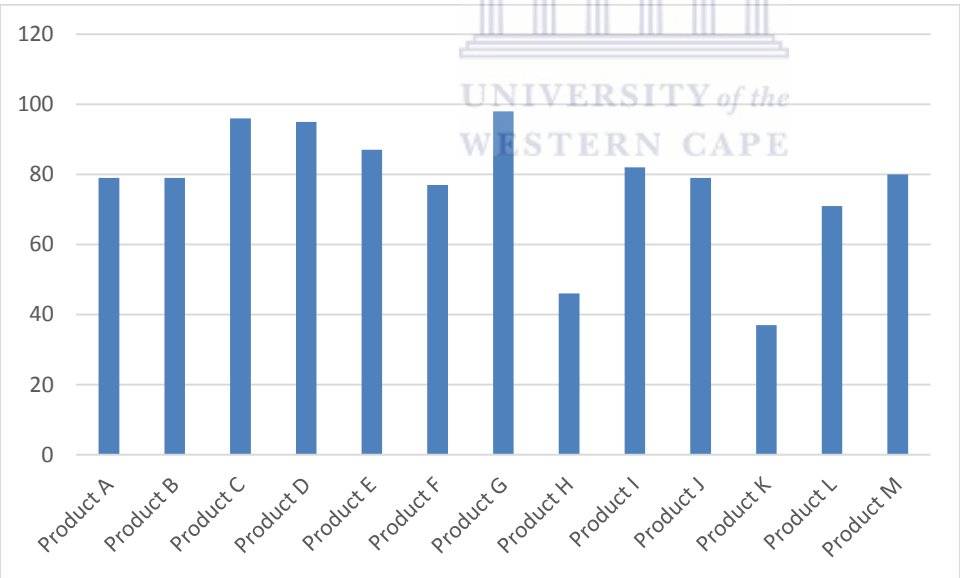

Figure 4-7 Percentage compliance of each product with Regulations 8 and 9 of Act 101 of 1965.

5 Conclusions

5.1 Quality

The study of the monographs affirmed the importance of composition, as a specific part of the herbal plant is required to achieve a product's intended therapeutic indications. Furthermore, the results of the literature search demonstrated that plant composition may have a direct impact on efficacy. However, due to a lack of information about the composition of the products in this study, it was difficult to determine quality compliance with the corresponding monograph. Therefore, CM companies applying for registration will need to submit detailed and accurate information about product composition. In turn, regulators will be responsible for verifying this information before approving product registration.

Some of the products presented conflicting data between the package inserts and labels. This demonstrated a poor quality of data presentation, and is not acceptable as inconsistent dosage or composition information will cause patient confusion. It also demonstrates that the applicant has poor control over its internal regulatory processes, which may be due to a lack of Good Manufacturing Practice (GMP). Applicants should ensure that product labelling does not provide conflicting information, and stricter regulatory labelling approval processes will need to be created and followed.

5.2 Efficacy

All the products were non-compliant with regard to indications because they contained therapeutic indications that were not stated in the monographs. While the literature

search provided some support for the flu indication, these studies would not satisfy the MCC's requirements. Applicants are required to conduct an extensive and well-balanced literature search when applying for evidence of efficacy, if efficacy cannot be obtained from a recognised source, such as the Martindale (MCC, 2013a).

Products were non-compliant with regard to posology. Underdosing could lead to a lack of efficacy, which could result in increased morbidity. Overdosing could result in toxicity and compromise patient safety.

5.3 Safety

Correct information with regard to contra-indications is essential for safety. On the one hand, it was promising to see that eleven of the thirteen products in the study were deemed compliant in reflecting the contra-indications as per the monographs. On the other hand, some products did not comply fully with the special warnings, such as the labels that did not contain the hepatotoxicity risk related to Pelargonium. Use of these products in susceptible patients could have detrimental consequences. Furthermore, product labelling without warnings could lead to a false perception of safety.

It was concerning to find that only two of the thirteen products complied fully with the monographs' information pertaining to pregnancy and lactation. Since all but one of the monographs stated that there was insufficient safety data to prescribe use during pregnancy and lactation, the product labelling should state that safety in this regard has not been established.

5.4 MCC Labelling Compliance

The MCC has mandated that CMs contain the statement that the CM has not been MCC-evaluated (MCC, 2013). Only 46% of the products in this study contained this statement. This is a significant non-conformance, since this requirement should have been implemented by May 2014 (MCC, 2013b).

The majority of the products complied only partially with the requirements of Regulation 8, and 77% of the products did not contain text in a language other than English. This poses a risk that patients who do not understand English could misuse the product. While these products were not required to comply with Regulation 8 at the time of this study, applicants will have to correct their labelling to align with the future requirements. All the products contained batch numbers (a necessary GMP requirement for product traceability), as well as expiry dates (which may affect product safety and efficacy).

Pharmacological classifications were provided for the majority of the products, but there were slight variations in the classification chosen. It must be considered that some of the products contained vitamins, minerals, and even other herbal ingredients not recognised by the EMA monographs. In such cases it would be difficult for the applicant to determine the appropriate pharmacological classification. It is recommended that the MCC provide CM companies with further guidance in the selection of correct pharmacological classifications. This could be done in a workshop or at a conference.

Based on the results of this study, CMs are not yet fully compliant with either the prescribed EMA monographs or the MCC's requirements. None of the products

investigated were compliant with the MCC's mandatory minimum labelling requirements. Applicants should urgently revise their product labelling to comply with the minimum labelling requirements.

The minimum labelling requirements are simpler to fulfil than those necessary for product approval. Therefore, if applicants are unable to meet these requirements, there is a likelihood that they will struggle to provide the complex data required for product registration.

Further research should be conducted regarding the challenges faced by the CM industry in obtaining the data they require for MCC evaluation and approval. It would also be beneficial to investigate what challenges the MCC faces in evaluating CM submissions. The CM industry and the MCC are encouraged to work together in this multifaceted challenge of CM regulation, to assure that marketed Complementary Medicines are of a suitable quality, are safe, and are effective.

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7 Appendices

7.1 Appendix 1: Research Proposal

Title

An evaluation of Western Herbal Complementary Medicine labelling in South Africa, to determine whether the product labelling information complies with established herbal monographs and whether it meets local regulatory requirements.

Introduction

In South Africa, Complementary Medicines (CMs) have come under increased scrutiny in the past few years. CMs are widely used by the South African public (MCC, 2013), and in 2013 the South African Medicines Control Council (MCC) published guidelines to improve the regulation of these products (MCC, 2013). An important component of these guidelines pertains to labelling requirements. Product labelling includes the container labels, package inserts and patient information leaflets. Appropriate labelling is necessary to provide consumers with information on how to use the product correctly and safely.

Western Herbal Medicines is categorised as a CM discipline (MCC, 2013). This research project aims to study the labelling of selected Western Herbal Medicines. Specifically, products falling under the category of “immune boosters” will be studied. The MCC has classified immune boosters under 32.16 (Other) and requires that these comply with the CM guidelines by May 2016 (MCC, 2013).

The labelling of the products selected will be assessed to determine whether pertinent information such as the indications, recommended dosages, contra-indications and side effects is in accordance with recognised herbal monographs. The labelling will also be assessed for compliance with the MCC’s regulatory requirements. The data obtained

from this research will provide further information into the current status of Western Herbal Medicine labelling compliance.

Methodology

Literature Search

A literature search will review the MCC's current CM guidelines, and the Medicines and Related Substances Act (Act No. 101 of 1965), to establish the requirements for the labelling of CMs. The European Medicines Agency (EMA) database of Community Herbal Monographs will be searched to obtain the relevant herbal monographs for the active ingredients contained in the products identified in this study.

Demographic Area

The demographic area chosen for this study is the Northern Suburbs of Johannesburg. These suburbs are close to the Johannesburg and Sandton CBDs as well as the middle-class suburbs. There is a wide selection of large-chain pharmacies as well as smaller, privately owned pharmacies and health shops in these areas. These contain a wide selection of the various marketed brands of Western Herbal Medicines, and therefore the inclusion of these stores will provide a broad sample of the immune-boosting Western Herbal Medicines required for this study.

Product Selection

The inclusion criteria of the products selected will include labelling which indicates that the product may be used for immune-enhancing effects, and contains one or more active ingredients listed in the EMA community herbal monographs, as these are recognised by the MCC (MCC, 2013).

Labelling Assessment

A labelling assessment form will be created based on the MCC's requirements. This form will reference the information prescribed in the corresponding EMA herbal

monograph in order to compare it with the product's information. The assessment form will also include the information that the MCC requires all CM labelling to have with immediate effect, as well as the information that will be required by the May 2016 deadline.

Each product will be recorded on the data collection checklist using the product's trade name, and its corresponding labelling information will also be captured. The collected data will be then be analysed in order to determine the percentages of products in the sample that complied or did not comply with the various labelling requirements. These results will provide a conclusion as to the current status of labelling compliance of Western Herbal CMs.

Ethical Considerations

The labelling assessment form will be submitted to the Ethics Committee for approval. This research does not involve patients nor healthcare professionals, therefore ethical approval for research subjects is not required. However, there are still ethical issues to consider regarding the promotion and marketing of these products. The names of the pharmacies and health shops from which products are bought will be kept confidential. However, the proprietary names of the products obtained will be used, as this information is freely available within the public domain. Furthermore, the results obtained are for the sole purpose of obtaining the information required for this research topic, and have no association with the promotion nor disparagement of the products. The manufacturing companies producing the products have no involvement with this research project and this research has no financial interests.

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7.2 Appendix 2: Data Collection Tool

Western Herbal Complementary Medicines Labelling Assessment Form

Trade Name:

Active Ingredient/s:

1. **EMA Herbal Monograph:**

   Date of compilation/last revision:

Heading	EMA Herbal Monograph	Product Label	Complies	Non-Compliant
Qualitative and quantitative composition				
Pharmaceutical Form				
Therapeutic indications				
Posology				
Duration of use				

Heading	EMA Herbal Monograph	Product Label	Complies	Non-Compliant
Method of administration				
Contraindications				
Interactions with other medicinal products and other forms of interaction				
Pregnancy and lactation				
Effects on ability to drive and use machines				
Undesirable effects				
Overdose				

Comments: (Does the product comply with the information prescribed by the EMA monograph?)

2. MCC prescribed minimum information (Required to have been implemented by 15 May 2014)

Criteria	Information on Label (Provide Description)	Complies	Non-Compliant
Written in English and at least one other official language			
Category of medicine			
Pharmacological classification of the medicine			
Discipline of medicine			
The words “This medicine has not			

Criteria	Information on Label (Provide Description)	Complies	Non-Compliant
been evaluated by the Medicines Control Council. This medicine is not intended to diagnose, treat, cure or prevent any disease"			
All claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner"			
No medicinal claims: Immediate label			
Carton			
Package Insert			
Patient Information Leaflet			

Comments: (Does the product comply with the minimum mandatory labelling information?)

3. Labelling Requirements in terms of Medicines and Related Substances Act, 1965

Label Criteria	Information on Label (Provide Description)	Complies	Non-Compliant
Label (Regulation 8 of the Act)			
Present/Absent			
Affixed to immediate container			
Clearly legible indelible letters in English			
Clearly legible indelible letters in at least one other official language			
Scheduling status (where applicable)			
Proprietary name of the medicine			
Registration/Reference Number			

Label Criteria	Information on Label (Provide Description)	Complies	Non-Compliant
Dosage form			
Approved name of each active ingredient of the medicine			
Quantity thereof contained in a dosage unit, or per suitable mass or volume or unit			
Name and percentage of any bacteriostatic or bactericidal agent which has been added to the medicine as a preservative			
Approved name of any anti-oxidant contained in the medicine			
Quantity of sugar contained in the medicine			
Quantity of ethyl alcohol contained in the medicine, expressed as a percentage of the total volume of the medicine if such quantity exceeds two per cent by volume			
Content of the medicine package expressed in the appropriate unit or volume of the medicine			
Approved indications for use of the medicine			
Recommended dosage of the medicine			
Where applicable, the instruction 'Shake the bottle before use'			
Lot number			
Expiry date			
Name of the holder of certificate of registration (or name of applicant)			

Label Criteria	Information on Label (Provide Description)	Complies	Non-Compliant
Storage temperature and other precautions required for the preservation of the medicine			
The warning: 'Keep out of reach of children'			
If the medicine contains TARTRAZINE, the warning: 'Contains TARTRAZINE'			
Carton (where applicable)			
Clearly legible indelible letters in English			
Clearly legible indelible letters in at least one other official language			
Scheduling status (where applicable)			
Proprietary name of the medicine			
Registration/Reference Number			
Dosage form			
Approved name of each active ingredient of the medicine			
Quantity thereof contained in a dosage unit, or per suitable mass or volume or unit			
Name and percentage of any bacteriostatic or bactericidal agent which has been added to the medicine as a preservative			
Approved name of any anti-oxidant contained in the medicine			

Label Criteria	Information on Label (Provide Description)	Complies	Non-Compliant
Quantity of sugar contained in the medicine			
Quantity of ethyl alcohol contained in the medicine, expressed as a percentage of the total volume of the medicine if such quantity exceeds two per cent by volume			
Content of the medicine package expressed in the appropriate unit or volume of the medicine			
Approved indications for use of the medicine			
Recommended dosage of the medicine			
Where applicable, the instruction 'Shake the bottle before use'			
Lot number			
Expiry date			
Name of the holder of certificate of registration (or name of applicant)			
Storage temperature and other precautions required for the preservation of the medicine			
The warning: 'Keep out of reach of children'			
If the medicine contains TARTRAZINE, the warning: 'Contains TARTRAZINE'			
Package Insert (Regulation 9 of the Act)			
Present/Absent			
Clearly legible text in English			

Label Criteria	Information on Label (Provide Description)	Complies	Non-Compliant
Clearly legible text in at least one other official language			
Scheduling status (where applicable)			
Proprietary name and dosage form			
The approved name of each active ingredient Quantity thereof contained in a dosage unit or per suitable mass or volume or unit of the medicine			
The approved name and quantity of any bactericidal or bacteriostatic agent included in the medicine as a preservative , expressed as a percentage			
The quantity of ethyl alcohol included in a preparation for oral or parenteral administration, if such quantity exceeds two per cent by volume			
The words " contains TARTRAZINE" should the medicine contain such ingredient			
"contains sugar" or "sugar free" whichever is applicable			
Pharmacological classification			
Pharmacological action			
Indications			
Contra-indications			
Warnings			
Interactions			

Label Criteria	Information on Label (Provide Description)	Complies	Non-Compliant
Pregnancy and lactation			
Dosage and directions for use			
Side effects and special precautions			
Known symptoms of over dosage and particulars of its treatments			
Identification			
Presentation			
Storage instructions, including storage temperatures			
Reference number (where applicable) followed by the expression " Act 101/1965"			
Name and business address of the holder of the certificate of registration/applicant			
Date of publication of the package insert (where applicable)			
Patient Information Leaflet (Regulation 10 of the Act)			
Present/Absent			
Scheduling status			
Proprietary name and dosage form			
The composition of the medicine			
The approved indications and use			
Instructions on how to take the medicine, including:			
Contra-indications			

Label Criteria	Information on Label (Provide Description)	Complies	Non-Compliant
Precautions			
Warnings (e.g. concerning sedative properties of the medicine or risks involved with sudden withdrawal of the medicine)			
Interactions			
The following general statements: "If you are taking medicines on a regular basis, using the medicine at the same time with another medicine may cause undesirable interactions. Please consult your doctor, pharmacist or other health care professional for advice." "If you are pregnant or breast feeding your baby while taking this medicine please consult your doctor, pharmacist or other health care professional for advice.			
Instructions on how to take the medicine, including the following statements: "Do not share medicines prescribed for you with any other person. " "In the event of over dosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre"			
Side effects, including the following general statement: "Not all side-effects reported for this medicine are included in			

Label Criteria	Information on Label (Provide Description)	Complies	Non-Compliant
this leaflet. Should your general health worsen while taking this medicine, please consult your doctor, pharmacist or other health care professional for advice"			
Storage and disposal information, including the following general statement: "store all medicines out of reach of children."			
Presentation, which includes the number, volume or mass per package unit and a description of the packaging material, e.g. bottle, blister pack, etc			
Identification of the medicine, i.e. the description of its physical appearance as tablet, capsule, etc			
Registration number of the medicine			
Name, business address and telephone number of the holder of the certificate of registration/applicant			
Date of publication of the patient information leaflet			

Comments: (Does the product comply with the Labelling requirements of the Medicines Act? Product will be required to demonstrate compliance by latest May 2016)

7.3 Appendix 3: Criteria used to assess percentage of compliance

Compliance with EMA monographs

Variable Included	Variable Excluded	Reason for exclusion
Pharmaceutical Form	Qualitative and quantitative composition	Not all products could be determined as there is not sufficient quality related data available
Therapeutic indications	Pharmaceutical Form	Not all products could be determined as there is not sufficient quality related data available
Posology		
Duration of use		
Method of administration		
Contraindications		
Special warnings and precautions for use		
Interactions with other medicinal products and other forms of interaction		
Pregnancy and lactation		
Effects on ability to drive and use machines		
Undesirable effects		
Overdose		

Compliance with MCC minimum prescribed requirements

Variable Included	Variable Excluded	Reason for exclusion
The words “This medicine has not been evaluated by the Medicines Control Council. This medicine is not intended to diagnose, treat, cure or prevent any	Written in English and at least one other official language	Evaluated in the section of compliance with Regulation 8.

disease”		
All claims relating to symptoms must be accompanied by the advice “If symptoms persist consult your healthcare practitioner”	No medicinal claims	Only the immediate labels of two products did not comply with this.
Category of medicine		
Pharmacological classification of the medicine		
Discipline of Medicine		

Compliance with Regulation 8 of Act 101 of 1965 (Label)

Variable Included	**Variable Excluded**	**Reason for exclusion**
Immediate container label only	Outer container label	Not all products contained one
Present	Approved name of any anti-oxidant contained in the medicine	Could not be determined if the products contained these ingredients, therefore this was not applicable to all products
Affixed to immediate container	Quantity of sugar contained in the medicine	
Clearly legible indelible letters in English	Quantity of ethyl alcohol contained in the medicine, expressed as a percentage of the total volume of the medicine if such quantity exceeds two per cent by volume	
Clearly legible indelible letters in at least one other official language	If the medicine contains TARTRAZINE, the warning: 'Contains TARTRAZINE’	
Scheduling status (where applicable)	Where applicable, the instruction 'Shake the bottle before use'	Not applicable to oral solid dosage forms
Proprietary name of the medicine		

Variable Included	Variable Excluded	Reason for exclusion
Registration/Reference Number		
Dosage form		
Approved name of each active ingredient of the medicine		
Quantity thereof contained in a dosage unit, or per suitable mass or volume or unit		
Name and percentage of any bacteriostatic or bactericidal agent which has been added to the medicine as a preservative		
Content of the medicine package expressed in the appropriate unit or volume of the medicine		
Approved indications for use of the medicine		
Recommended dosage of the medicine		
Lot number		
Expiry date		
Name of the holder of certificate of registration (or name of applicant)		
Storage temperature and other precautions required for the preservation of the medicine		
The warning: 'Keep out of reach of children'		

Compliance with Regulation 9 of Act 101 of 1965 (Package Insert)

Variable Included	Variable Excluded	Reason for exclusion
Clearly legible text in English	The quantity of ethyl alcohol included in a preparation for oral or parenteral administration, if such quantity exceeds two per cent by volume	Not applicable to all of the products
Clearly legible text in at least one other official language	The words " contains TARTRAZINE" should the medicine contain such ingredient	
Scheduling status (where applicable)	Pharmacological classification	Discussed separately
Proprietary name and dosage form		
The approved name of each active ingredient		
Quantity thereof contained in a dosage unit or per suitable mass or volume or unit of the medicine		
"contains sugar" or "sugar free" whichever is applicable		
Pharmacological action		
Indications		
Contra-indications		
Warnings		
Interactions		
Pregnancy and lactation		
Dosage and directions for use		
Side effects and special		

Variable Included	Variable Excluded	Reason for exclusion
precautions		
Known symptoms of over dosage and particulars of its treatments		
Identification		
Presentation		
Storage instructions, including storage temperatures		
Reference number (where applicable) followed by the expression " Act 101/1965"		
Name and business address of the holder of the certificate of registration/applicant		
Date of publication of the package insert (where applicable)		