DEVELOPING A REGIONALLY RECOGNISED FRAMEWORK TO SUPPORT REGULATORY HARMONISATION OF LABELLING REQUIREMENTS IN THE SOUTHERN AFRICA DEVELOPMENT COMMUNITY (SADC)

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Declaration

I, Givemore Mushayi, declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Master of Science in Medicine (Pharmaceutical Affairs) at the University of the Witwatersrand, Johannesburg. It has not been presented before for any degree or examination at any other University.

6th day of November 2019,

Johannesburg

Abstract

Worldwide, medicine regulatory agencies are intentionally pursuing the concept of harmonisation or convergence of regulatory requirements across countries, Regional Economic Communities (RECs) and in some cases across continents. For Africa, the New Partnership for Africa's Development (NEPAD), an organ of the African Union, is coordinating REC specific medicines regulatory harmonisation projects. The SADC Medicines Regulatory Harmonisation project has made significant progress. To date, registration guidelines and other technical guidelines have been published and are being adopted by member states.

Following the adoption of the Zazibona process, different facets of regulatory harmonisation are being implemented, including work sharing in the form of joint dossier assessments and manufacturing facility inspections. Despite these developments, the harmonisation of medicine labelling requirements within the region has been lagging behind with ramifications on the accessibility of essential medicines for patients.

A comparative analysis of the legislative and regulatory landscape within the SADC region showed that the primary barrier to harmonisation of labelling requirements was the country-specific prescribed statutory requirements which are contradictory or unique and in some cases congruent. A harmonised labelling conceptual framework is proposed which attempts to resolve the conflicting and unique requirements. A panel of experts and stakeholders reviewed the proposed concept through a prospective survey. The majority of respondents agreed in principle with the proposed framework, where concerns were raised, necessary changes were made to address queries raised in the review. All the stakeholders were agreeable to the implementation of the proposal as an interim measure while changes to regulations are being considered. These changes to regulations were estimated to be achievable in less than four years.

Given the potential impact of harmonising labelling requirements on public health, control of pharmaceutical products and accessibility of essential medicines, the SADC secretariat may use the outcome of this study for wider engagement within SADC member states to expedite harmonisation of labelling requirements.

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Table of Contents

Declaration ... ii

Acknowledgements ... iv

Table of Contents ... v

List of Figures ... 1

List of Tables ... 2

Abbreviations ... 3

1. Introduction and literature review ... 5

Background ... 5

1.1.1. Harmonisation and access to medicines ... 5

1.1.2. Regulatory harmonisation – Global initiatives ... 6

Harmonisation vs Convergence ... 6

European Union Harmonisation ... 7

International Council for Harmonisation ... 7

African Medicine Regulatory Harmonisation ... 8

African Union Model Law on Medical Products Regulation ... 12

SADC Regulatory Harmonisation ... 13

Problem Statement: The need for harmonisation of labelling requirements ... 15

Study Aim ... 16

Study Objectives ... 17

Objective 1: Comparative analysis of legislative and regulatory systems in selected SADC counties ... 17

Objective 2: Development of a harmonised labelling conceptual framework ... 17

Objective 3: Stakeholder assessment and validation of the harmonised labelling framework. ... 17

2. Methods ... 18

2.1. Summary of methods used ... 18

2.1.1. Qualitative comparative analysis ... 19

2.1.2. Framework Development ... 20

2.1.3. Stakeholder and Expert assessment & validation ... 20

Design and Piloting of the Questionnaire ... 20

Distribution of Questionnaire ... 21

2.2. The justification for Method Used ... 21

2.3. Inclusion criteria for selected SADC stakeholders: ... 22

2.4. Data collection and analysis ... 23

2.5. Ethics ... 23

2.6. Limitations ... 23

3. Comparability analysis of legal requirements ... 24

3.1 The Legal and Regulatory Landscape ... 24

3.2 Comparative analysis of the requirements for labelling components: ... 28

3.2.1 Comparison of requirements for immediate container labels and cartons: 28
3.2.2 Comparison of requirements for Blister labels: 37
3.2.3 Comparison of requirements for Package Inserts: 39
Comparison of the Format of Package inserts 39
The content of the package insert 47
3.2.4 Assessment of scheduling requirements 49
4. Proposal for the harmonised labelling 50
4.1. The harmonised label concept 51
***4.1.1. Prototypes of the label(s): Immediate container label prototype* 53**
***4.1.2. Prototypes of the label(s): Carton prototype – version* 1 54**
***4.1.3. Prototypes of the label(s): Carton prototype – version 2* 55**
***4.1.4. Prototypes of the label(s): Other Labels:* 56**
4.2. The Harmonized Package insert concept 57
***4.2.1. Harmonising conflicting and unique requirements* 57**
***4.2.2.* Harmonising the structure of the Package insert 59**
***4.2.3.* Harmonisation of the content of the package insert 60**
***4.2.4. Lifecycle management to the content of the package insert / SMPC* 61**
5. Stakeholder assessment of the harmonised labelling concept 62
5.1. Acceptance of the label harmonisation framework 64
5.2. Acceptance of the Package insert harmonisation framework 68
5.3. Changing the legal landscape to bring harmonisation 71
5.4. The potential impact of regulatory harmonisation in SADC 73
6. Discussion and Conclusion 77
References 79
Appendix 1 – Ethics Approval 84
Appendix 2 – Plagiarism Declaration 85

List of Figures

Figure 1: AU Vision for regulatory harmonisation[27] 9
Figure 2, REC participating in the AMRHi 10
Figure 3: Summary of the key facets captured by the AU model law: Source: UNDP[31] 13
Figure 4: Immediate container label prototype 53
Figure 5: Carton prototype – version 1 54
Figure 6: Carton – Version 2 prototype 55
Figure 7: Blister Label prototype 56
Figure 8: Semisolids (<5g) label prototype 56
Figure 9: Vials / Ampoules (<5ml) prototype 56
Figure 10: Countries represented in the study 62
Figure 11: Role of respondents in the NMRA 63
Figure 12: Acceptability of naming convention on labelling 64
Figure 13: Acceptability of position and identification of schedules 65
Figure 14: Acceptability of registration number panel 66
Figure 15: Countries with provisions for accepting additional information on labels 66
Figure 16: Applicability of interim provisions to expedite harmonisation 67
Figure 17: Acceptability of EU Package Insert / SMPC Structure as a reference for harmonisation 68
Figure 18: Acceptability of the format of presenting regulatory information on the Package insert 69
Figure 19: Acceptability of SAHPRA content guidelines as a reference for content harmonisation 69
Figure 20: Acceptability of SAHPRA approved Package insert as reference 70
Figure 21: Declaration of will to initiate changes 71
Figure 22: Regulatory & Legal changes required to facilitate harmonisation 72
Figure 23: Timelines for changes in the regulatory landscape 72
Figure 24: Scale for measuring perception 73
Figure 25: Potential impact of harmonisation on Public Health 73
Figure 26: Potential impact of harmonisation on public health in the selected countries 74
Figure 27: Potential impact of harmonisation on the accessibility of essential medicines 74
Figure 28: Potential impact of harmonisation on parallel importation 75
Figure 29: Ability of the harmonised framework to curb the illegal trade of medicines 75
Figure 30: Potential impact of harmonisation on the counterfeiting of medicines in SADC 75
Figure 31: Adequacy of measures to curb counterfeiting in the harmonised framework 76
Figure 32: Impact on control of habit forming drugs 76

List of Tables

Table 1: AMRHi Projects (Dec 2016) 11
Table 2: Summary of the regulatory landscape governing labelling of pharmaceuticals 24
Table 3: Comparison of requirements for immediate container labels and cartons 29
Table 4: Comparison of requirements for Blister labels 37
Table 5: Comparison of requirements for Package Inserts 39
Table 6: Accepted references for package insert content 47
Table 7: Summary -Comparison of Schedules/categories of distribution 49
Table 8: Description & Discussion of the harmonised label concept: Label 51
Table 9 Description of harmonised Package inserts 57
Table 10: Format for the proposed harmonised leaflet 59

Abbreviations

AMA	African Medicines Agency
AMRH	African Medicines Regulatory Harmonisation
AMRHI	African Medicines Regulatory Harmonisation Initiative
AU	African Union
AUC	African Union Commission
CEMAC	Central African Economic and Monetary Community
CTA	Clinical trials authorization
CTD	Common Technical Document
EAC	East African Community
ECOWAS	Economic Community of West African States
eCTD	Electronic Common Technical Document
EMA	European Medicines Agency
EU	European Union
EWG	Environmental Working Group
FDC	Fixed Dose Combination
FPP	Finished Pharmaceutical Product
GMP	Good Manufacturing Practices
HCR	Holder of a Certificate of Registration
HICs	High-income countries
HIV	Human Immunodeficiency Virus
ICDRA	International Conference of Drug Regulatory Authorities
ICH	International Council for Harmonisation
IGAD	Inter-governmental Authority on Development
IMS	Information Management System
LMICs	Low- and middle-income countries
MA	Marketing Authorisation
MCAZ	Medicines Control Authority of Zimbabwe
MCC	Medicines Control Council
MRH	Medicines Registration Harmonisation
NEPAD	New Partnership for Africa's Development
NMRA	National Medicines Regulatory Authority
NMRC	Namibia Medicines Regulatory Council

OCEAC	Organization of Coordination for the Fight against Endemic Diseases in Central Africa
QMS	Quality Management System
QSE	Quality Safety and Efficacy
REC	Regional Economic Cooperation
RSA	Republic of South Africa
SADC	Southern African Development Community
SAHPRA	South African Health Products Regulatory Authority
SARPAM	Southern Africa Regional Programme on Access to Medicines and Diagnostics
SRA	Stringent Regulatory Authority
STD	Sexual Transmitted Disease
USFDA	United States Food and Drug Administration
WAEMU	West African Economic and Monetary Union
WAHO/UEMOA	West African Health Organisation – West African Economic and Monetary Union
WHO	World Health Organisation
ZAMRA	Zambian Medicines Regulatory Authority

1. Introduction and literature review

Background

1.1.1. Harmonisation and access to medicines

Rehman, Arfons and Lazarus[1] noted that the thalidomide and other drug-related tragedies had led to a rapid transformation of medicine regulation by the United States Food and Drug Administration (USFDA). This, in turn, led to a change in national medicine legislative frameworks across the globe we see today, which has been extensively discussed by Rägo and Santoso.[2] In a study by Ratanawijitrasin and Wondemagegnehu, these developments were coined "crisis led drug regulation reforms", and these reforms were observed in all the major regions of the world.[3] From these developments, the role of National Medicines Regulatory Authorities (NMRAs) in ensuring not just access, but access to efficacious, quality and safe essential medicines for the public has been fully established.[2]

Notwithstanding the developments in medicine regulation globally including in developing countries, access to essential medicines remains a problem in many countries. Since 1977, the World Health Organisation (WHO) has been actively promoting the implementation of the essential medicines concept in member states to address some of the challenges related to access to medicines.[5] Santoso *et al.* [4] stated that about a third of the world population still has no adequate access to essential medicines. The reasons for this lack of access have been extensively documented in various studies and reports.[4, 5] The WHO[6] has also reported on an array of issues in the African medicine regulatory structures and framework that contribute to the lack of access to essential medicines. A situational analysis by Ndomondo-Sigonda *et al.* pointed out the following key issues which NMRAs in the SADC region are facing and which have a considerable impact on access to quality, safe and efficacious medicines[7];

- Inefficient processes resulting in delays in the registration of medicines
- Resource limitations in the implementation of effective medicine regulation
- Lack of capacity in the NMRAs to effectively monitor the safety, quality and efficacy of medicines at country level

Inaccessibility to quality essential medicines has resulted in the entrance of counterfeit products in the supply chain of some African countries.[8, 9]

Regulatory harmonisation is one of the mechanisms that seeks to address some of these issues if the following is realised;

- The implementation of common regulatory requirements and standards for inspection and evaluation: This will facilitate the sharing of information and collaboration between authorities to reduce duplication of efforts.[6, 10]
- Use of common data sets for registration by use of common technical documents: This will reduce the burden on the manufacturers / applicants as they will have a common data pack for all countries. Different regulatory requirements on developmental studies make it a prohibitively costly exercise, impacting highly on the availability and accessibility of essential medicines.[11]
- Use of standardised labelling for medicinal products: This is important for supply chain management issues. Manufacturers can produce medicines with common labels for various countries. Harmonised labelling of medicines has both logistical and cost benefits to all stakeholders and promotes pooled procurement in SADC.[12, 13]

If the common goals above are achieved, regulatory harmonisation will significantly benefit all stakeholders whose common objective is to ensure availability and accessibility of safe, efficacious and quality medicines.[6]

1.1.2. Regulatory harmonisation – Global initiatives

Harmonisation vs Convergence

At a global level, a number of NMRAs have embarked on a path of regulatory *harmonisation* and in some instances regulatory *convergence*.[14] The term 'Regulatory harmonisation' is defined as the process by which regulatory and scientific guidelines are developed to be identical across participating countries or regions[14]. The term "Regulatory convergence," on the other hand, represents a process whereby the regulatory and scientific guidelines across countries or regions become more similar or "aligned" over time[15]. Convergence is achieved by a gradual adoption or adaptation of policies, procedures, standards, scientific principles or guidelines, that are internationally recognised by individual countries[15]. Wider application across countries brings alignment of the regulatory framework to achieve a common public health goal.[15] In convergence, the harmonisation of laws and regulations is not required, countries align with each other gradually resulting in greater regulatory cooperation.[16] Regulatory convergence could have similar outcomes to harmonisation and should be considered where outright harmonisation activities are difficult to implement.

European Union Harmonisation

Regulatory harmonisation has been achieved in the European Union (EU) through adoption of the same rules and laws by member states, largely aimed at removing technical obstacles to trade.[17, 18] The harmonisation work relating to pharmaceutical products [Regulation 726/2004, see section 17.3.7] resulted in the formation of the single market for health commodities and in the establishment of the European Medicines Agency (EMA).[18] Therefore, harmonisation in Europe is one of the best cases achieved globally through establishing the same statutory requirements, standards and procedures for pharmaceutical products (Directive 2001/83/EC) by member states (*including labelling requirements*).

EMA has an important responsibility of implementing this directive throughout the EU. The Agency's success can be attributed to the availability and coorperation of skilled and experienced resources for the regulation of health products.[19] In the EU network, countries leverage on the capacity provided by fellow member states. Besides the work sharing or joint evaluations arrangements through the centralised procedure, EMA also coordinates activities at country level such as mutual recognition, decentralised medicines registration, and some aspects regarding clinical trials regulation.[19] These, among other factors, have made regulatory harmonisation in the EU to be recognised globally as a success and a reference point for regional regulatory harmonisation initiatives in various Regional Economic Communities (RECs), including the SADC regulatory harmonisation project.

International Council for Harmonisation

The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), formely known as the International Conference on Harmonisation, is a unique project that was established in 1990[20]. The ICH consisted of regulatory authorities of the European Union, Japan and the United States as well as experts from the pharmaceutical industry in these three regions. Its initial thrust was to develop harmonised regulatory and scientific guidelines for the registration of new medicinal products, and hence facilitate new product development.[20]

Since the inception of ICH, technical guidelines covering Efficacy, Quality and Safety topics have been developed and are being implemented. [21] Dossier formats such as CTD and eCTD have been implemented allowing multiple submissions to be done using the same dataset / similar dossier forrmat. Of late, thrust towards greater harmonisation beyond the ICH region

has seen the adoption of the ICH guidelines by non-ICH countries (regulatory convergence), yielding additional benefits to both regulatory agencies and industry. In SADC, many of the member states have adopted the CTD /eCTD guidelines as well as most of the scientific guidelines.[21]

ICH, through its activities in the harmonisation of regulatory requirements across the EU, Japan and US, enabled the pharmaceutical industry to eliminate the need for country specific developmental work and therefore brought efficiencies to the product development process[22]. This had direct impact on the cost of product development, timelines for development and registration. The ICH process, was therefore instrumental in the acceleration of access by patients of quality and cost effective medicines, with significant pharmacoeconomic gains.[22] Reduced cost of development allowed innovative companies to redirect their cost savings to new projects that will produce the ground-breaking therapies of the future.[22] In the context of SADC, the adoption of ICH standards and guidelines is currently helping in the regional cooperation and work sharing agreements such as Zazibona[22]

African Medicine Regulatory Harmonisation

Ensuring the availability of safe, good quality and reasonably priced medicines has been a challenge for many African countries for a very long time. Marketing authorisation (MA) and clinical trials authorisation (CTA) for global health products such as vaccines and medicines in many low- and middle-income countries (LMICs) have experienced delays ranging from 4-7 years in comparison to most of the high-income countries (HICs).[23, 24]

In Africa, barriers causing these delays include weak regulatory systems and standards, as well as divergent requirements across countries, lengthy medicine registration processes that lead to delays in medicine availability, technical capacity and capability constraints, overall human and financial resource constraints; and failure to leverage regulatory decisions by better-resourced regulatory authorities and the World Health Organization (WHO). In addition, delays in clinical trials authorisation (CTA) have been attributed mainly to the lack of technical capacity as well as role clarity and transparency between national medicines regulatory authorities (NMRAs) and national ethics committees (NECs).[24]

The establishment of the African Medicines Regulatory Harmonisation Initiative (AMRHi) in

2009 was driven by the need to remove these barriers that hinder patient access to medicines and healthcare products in Africa.[25] The AMRHi is a regulatory systems strengthening project of the New Partnership for Africa's Development (NEPAD), an agency of the African Union (AU). The AMRH initiative aims to support African countries to overcome the constraints discussed above by building effective medicines regulation and registration systems through regional harmonisation and capacity building.[26] In this process, AMRHi seeks to establish and improve standards and requirements related to the regulation of and access to safe, high-quality medicines for the African population.[26] The work done by the AMRHi serves as a foundation for the establishment of the African Medicines Agency (AMA) [23].

The African Medicines Agency (AMA) will be an organ of the AU whose objective is to;

> "*promote the adoption and harmonisation of medical products, regulatory policies and standards, and scientific guidelines, and coordinate existing regulatory harmonisation efforts in the Regional Economic Communities and regional health organisations in Africa. It will further provide regulatory guidance, scientific opinion, and a common framework for regulatory actions on medical products, as well as priority, emerging issues and pandemics.*" [27]

The treaty paving the way to the formation of the AMA was signed in May 2018 following an undisputed decision by African ministers of health to adopt the agreement to establish an African Medicines Agency (AMA) after many years of deliberations[28] The AU's vision on the creation of AMA is illustrated below.

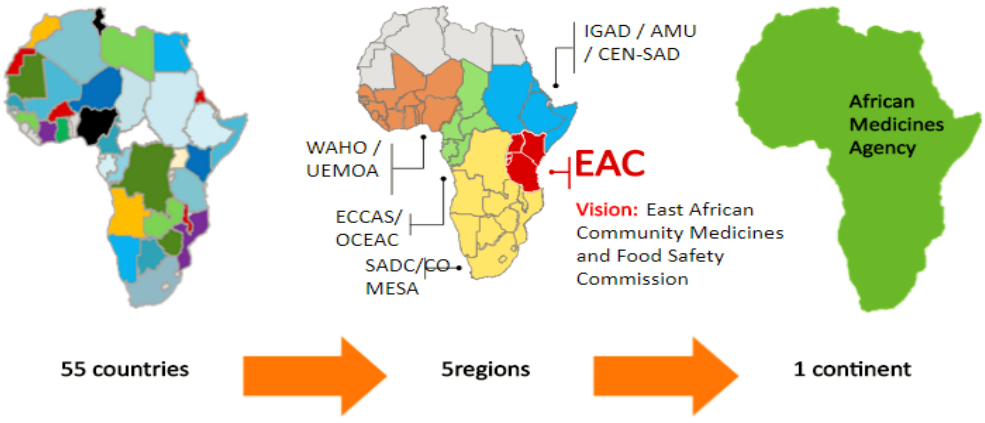


Figure 1: AU Vision for regulatory harmonisation[29]

To facilitate the convergence or harmonisation, the AMRHi is working with NMRAs within Regional Economic Cooperation (REC) schemes in Africa, therefore implementing the harmonisation projects in bite-sized chunks.[28] As of December 2016, 85 % of sub-Saharan Africa was covered with Medicine Regulatory Harmonisation (MRH) projects as illustrated below. [29]

RECs participating in the AMRHi [29]

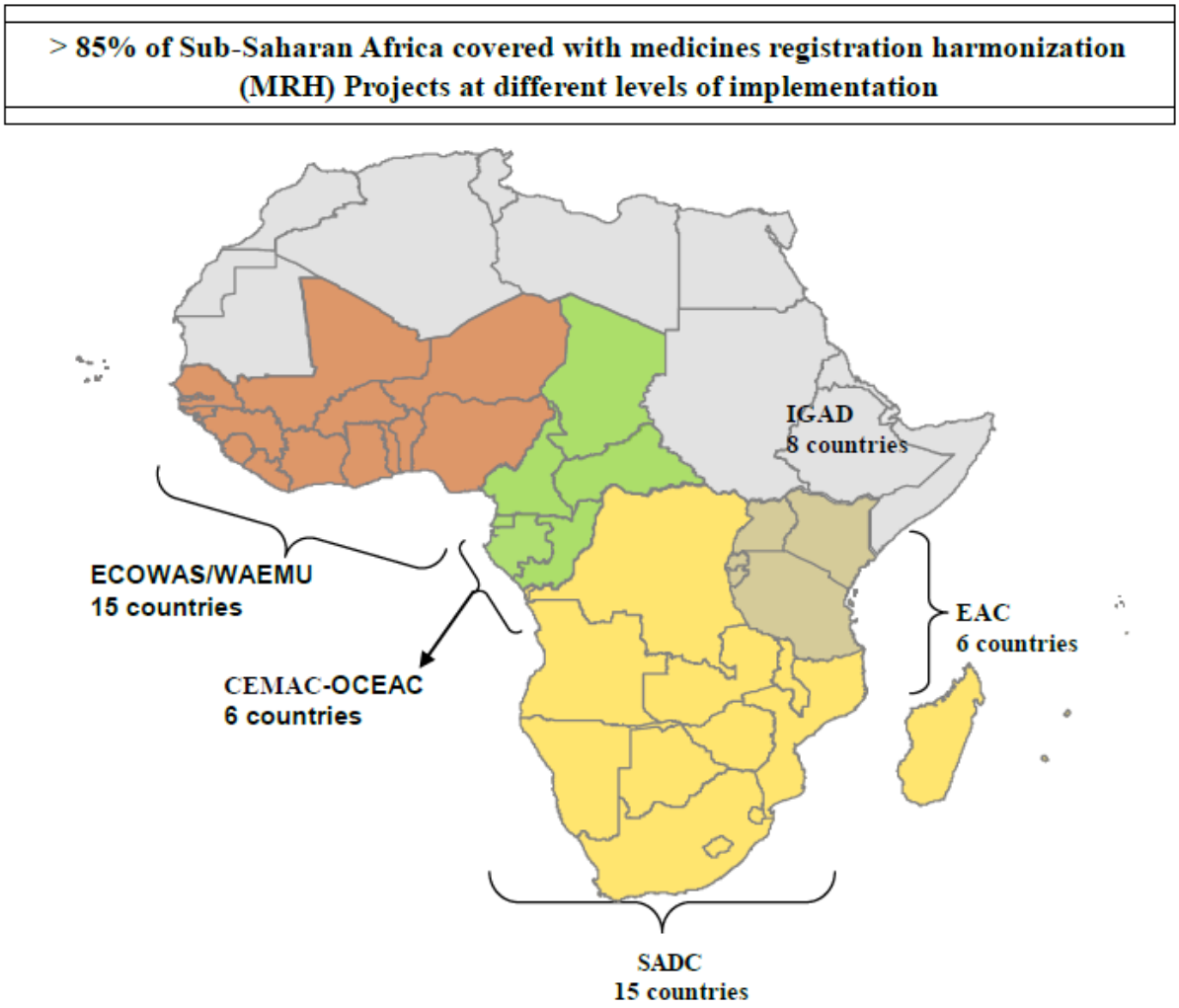


Figure 2, REC participating in the AMRHi[29]

Key:

CEMAC - The Economic and Monetary Community of Central Africa

EAC – East African Community

ECOWAS – Economic Community of West African States

IGAD - Intergovernmental Authority on Development

OCEAC - Organization of Coordination for the Fight against Endemic Diseases in Central

Africa

WAEMU – West African Economic and Monetary Union

SADC – Southern African Development Community

Note: *Most countries in Africa belong to more than one regional economic bloc*

The status of the AMRHi Projects as of December 2016 is given in the table below[29].

Table 1: *AMRHi Projects (Dec 2016)*[29]

REC	**Status**
East Africa EAC	Implementation: ▪ Launched March 2012 ▪ Harmonised standards (technical guidelines and requirements) approved by the Council of Ministers - Registration of medicines (based on CTD) - Good Manufacturing Practices (GMP) - Quality Management System (QMS) - Information Management System (IMS) ▪ Came into force from Jan. 2015, countries at different levels of implementation
CEMAC-OCEAC	In progress Central Africa: ▪ Regional pharmaceutical policy in 6 CEMAC Member States ▪ 1st MRH Project Steering Committee convened 15-16 November 2016
Southern Africa SADC	▪ March 2011: MRH Framework Agreed by SADC NMRAs ▪ October 2013 implementation of MRH Framework "Breakthrough Activities" under SARPAM Funding of Zazibona scheme ▪ 2014 Official Integration of Zazibona Scheme into SADC Framework for Regulatory Harmonisation ▪ 21-24 July 2015, SADC Regulators Forum Official Endorsement of Implementation of MRH

North/North- Eastern Africa	▪ Dec 2010: Consultation on AMRH ▪ 03-05 August 2015, Addis Ababa, Ethiopia: IGAD Conference of NMRAs and partners ▪ IGAD 2nd Regulators Meeting, Khartoum, Sudan, April 26-27, 2016 Preparatory stage
West Africa: ECOWAS and WAEMU	▪ ECOWAS and WAEMU launched a Medicines Regulatory Harmonisation (MRH) Project in February 2015 ▪ 1st Meeting of Joint MRH Project Steering Committee, February 2015 ▪ 2nd Steering Committee meeting, 20 April 2016 - Alignment of WAHO and WAEMU - Common Technical Document (CTD) - Development of the technical - requirements based on the harmonised CTD - Operationalisation of the 7 Expert - Working Groups (EWG) - Recruitment of MRH Project Staff

African Union Model Law on Medical Products Regulation

According to a SARPAM situational analysis performed in 2010, medicines harmonisation and accelerated access to efficacious and high-quality medicines in the AU Member States is constrained by lack of harmonised legal instruments.[7] The NEPAD Agency, working together with the African Union Commission (AUC) and Pan African Parliament developed a Model Law on Medical Products Regulation which was adopted by the AU Summit in January 2016.[30] The Model Law was drafted as a template for member states to update their current laws and subsequently establish semi- independent National Medicines Regulatory Authorities (NMRAs).[31] This law aims to lay a foundation for NMRAs on the African continent that will have the capability and capacity to ensure that only quality, safe, effective, cost efficient medicines are available and accessible to the general population in order to influence the health outcomes of every member state.[30] The summary below shows the major facets captured by the AU model law;

Figure 3: Summary of the key facets captured by the AU model law: Source: UNDP[31]

A principal feature of the Model Law is the harmonisation of regulatory standards and procedures to allow for more efficient marketing authorisation of medical products in the African region by outlining mechanisms for regional and sub-regional cross-registration and facilities inspections.[30] As discussed above, harmonisation or convergence of regulatory requirements (statutory instruments, scientific guidelines) by AU member states is a prerequisite to the formation and establishment of the African Medicines Agency. The model law above therefore provides a unique opportunity for member states to level the regulatory landscape. It is currently being used by member states to review existing legislation or establish new laws governing the regulation of medicines. Convergence towards common scientific standards is already on course with the adoption of ICH CTD / eCTD guidelines & specifications and scientific guidelines by various NMRAs.[22]

SADC Regulatory Harmonisation

The SADC Vision, coined in 1992, "*is to build a region in which there will be a high degree of harmonisation and rationalisation, to enable the pooling of resources to achieve collective self-reliance, to improve the living standards of the region's people.*"[32, 33]

Under the regional integration and collaboration objective, SADC established the SADC Pharmaceutical Programme in 1999. The programme was crafted to improve the ability of Member States to manage diseases of concern to public health in SADC, especially HIV

and AIDS, tuberculosis, and malaria.[33] Before long after the commencement of the Pharmaceutical Programme, SADC established the Protocol on Health in August 2004, with specific provisions (Article 29) for improving access, affordability, and effectiveness of pharmaceuticals within the region.[33] This was followed by the development of the **SADC Pharmaceutical Business Plan (2007 - 2013),** published in 2007 with the overall goal of ensuring availability of essential medicines. One of the key strategies to meet the above objective is strengthening regulatory capacity, supply, and distribution of essential pharmaceutical products through ensuring a fully functional regulatory authority with an adequate enforcement infrastructure.[34] Building on the regional harmonisation and integration momentum as given above, in 2011 SADC established the Medicine Registration Harmonisation project.

Within the framework of medicine regulatory harmonisation, the SADC Ministers for Health and Ministers for HIV and AIDs during their Joint meeting in November 2013, [35] approved the process to review and update the SADC Regional Registration Guidelines, which was achieved by streamlining them with international standards (ICH, WHO and FDA). The Ministers subsequently approved these updated Registration guidelines and CTD format in January 2015.[36] Member States are at various levels of adoption of these SADC Registration Guidelines at the national level. The use of a common CTD format and registration requirements is facilitating submission of similar applications for registration of medicines to various National Medicines Regulatory Authorities (NMRAs) within the region. It is also encouraging cooperation between NMRAs through work sharing initiatives.

Building on the success of the EAC MRH project which involved joint dossier assessments, the SADC region initiated a platform in 2013 called Zazibona, initially comprised of Zambia, Zimbabwe, Botswana and Namibia to coordinate the joint evaluations. The Zazibona process was established with a view of improving the availability of good-quality medicines through work-sharing in the evaluation of dossiers and the inspection of medicine manufacturing and testing facilities[37]. The aim was to significantly reduce the time taken to grant a MA in the individual countries, and ensure efficient utilisation of resources among NMRAs in the region through work sharing.[38,] In 2017, The Zazibona initiative evaluated 179 product applications over 15 meetings from October 2013 with a final decision reached for more than 90 products and a mean time to recommendation for registration estimated at nine months.[39, 40, 41] The Zazibona scheme was officially adopted as a SADC MRH Programme in 2014, a

total of ten (10) countries (including the four founding members) have now joined the scheme with different membership status as given below; South Africa, (active), Zimbabwe (active), Namibia (active), Zambia (active), Botswana (active) Swaziland (active), Democratic Republic of Congo (active), Angola (non-active), Seychelles (non-active) and Malawi (non-active).[41, 42]

Updating and harmonising regulatory standards to create one regional market and mutual recognition is one of the strategies included in the draft Strategy on Regional Manufacturing of Essential Medicines and Health Commodities (2016-2020). This strategy supports the pharmaceutical component in the SADC Industrialisation Strategy and Roadmap 2015 – 2063.[43] A harmonised regulatory framework including GMP certification is essential for speedy approval of new products, and will also result in a bigger market for locally produced products. Further to this, the **SADC** Medicines Regulators recognise the continued challenges with the registration of medicines by the pharmaceutical industry with respect to varying regulatory requirements within the region.[13] While the regional registration guidelines have been updated and a harmonised SADC CTD format approved, **the issue of product information and labelling and harmonised GMP requirements is still lagging.**

Problem Statement: The need for harmonisation of labelling requirements

In a study by Kirti, pharmaceutical companies expressed that country-specific registration and labelling requirements remain a barrier to market authorisations and distribution of medicines in African countries[13]. In particular, GMP inspections, GMP inspection fees and unique labelling laws at country level were given as the most critical problems.[13] The labelling problem is not peculiar to the pharmaceutical industry. Kapasila et al. concluded that the differences in country-specific labelling regulations and guidelines impacted significantly on the availability of certain food items across borders in South East Asia.[44] The situation in many countries is even worse for medical devices, where labelling information is not standardised and is disseminated through various media: videos, brochures, information leaflets, etc. This often confuses the patient as similar products' labelling is often entirely different.[45] Given the SADC Pooled procurement agenda, harmonisation of labelling is of great importance to enable the actual pooled procurement to be done in SADC.[46] To this end, the SADC Protocol on Health and the Pharmaceutical Business Plan emphasise the need for regulatory harmonisation including labelling.

Through the effort of different partners including WHO, AU, SADC members, NEPAD

(AMRHi), regulatory harmonisation in SADC is steadily progressing. Countries participating in the Zazibona initiative (Zambia, Zimbabwe, Namibia, Botswana and South Africa) have already converged towards harmonised technical requirements in the form of CTD. This has facilitated joint reviews by the participating countries. Notwithstanding these harmonisation efforts within SADC; the labelling harmonisation issue remains unsolved**. To date, there is no agreed framework to ensure harmonisation of labelling requirements within the region.**

The impact of the different requirements specified by individual countries **on the availability and accessibility of certain essential medicines has been well documented.**[13] In many cases, the single country product quantities needed are far less than the minimum batch sizes. In such cases, supply will be hindered to the detriment of the patients in need of such lifesaving medicines. If labelling harmonisation is achieved, pooled procurement could be enabled where one batch may be supplied to several countries. The economies of scale gained will benefit governments as well as patients. In this context, labelling harmonisation has a substantial public health benefit and should be prioritised by the SADC Medicine Regulation Harmonisation project.

Study Aim

The study is aimed at developing and presenting a proposed framework for regulatory convergence / harmonisation of product labelling requirements for SADC countries in order to improve the accessibility of safe, quality and cost-effective products in line with national medicine policies. The envisioned concept will take into account the importance of labelling information in ensuring the safe use of medicines and will not disregard policy matters enshrined in the national medicine policies (e.g. generic prescribing & dispensing). The underlying principles of rational medicine use will also be underpinned in the proposal.

Study Objectives

A systematic approach was used for the development of the harmonised product labelling framework by fulfilling the following objectives.

Objective 1: Comparative analysis of legislative and regulatory systems in selected SADC counties

The first part of the study was a review of the regulatory landscape in the selected SADC countries: South Africa, Zimbabwe, Namibia, Botswana and Zambia. The choice of countries considered in this study is discussed in detail in section 2.3. A comparative analysis of applicable legislation, regulations, and guidelines which govern labelling of pharmaceutical products in the selected countries was undertaken. Similarities and differences in the regulations and guidelines were identified and discussed. The comparative analysis identified the barriers to harmonisation such as differences in legal or regulatory requirements for the labelling of pharmaceutical products.

Objective 2: Development of a harmonised labelling conceptual framework

The second part of the study involved the development of a harmonised labelling conceptual framework to address the barriers to harmonisation such as differences in the legal requirements for labelling of pharmaceutical products.

Objective 3: Stakeholder assessment and validation of the harmonised labelling framework.

Various stakeholders (NMRA officers, regulatory experts, harmonisation leads in the AMRHi partners, independent consultants) were identified to evaluate the concept for acceptability, applicability, relevance, practicality and potential impact on the control of pharmaceutical products in SADC. The assessment by stakeholders validated the conceptual framework by confirming that it is acceptable and applicable to the SADC region.

2. Methods

2.1. Summary of methods used

In this study, the System Improvement Process methodology (SIP) [47] was adapted and used to develop the harmonised labelling framework. SIP methodology is a problem solving method that allows the main problem to be broken down into sub-problems. The sub-problems are then extensively analysed using appropriate research tools. Appropriate solutions to the sub-problems will then collectively solve the main problem. In this study, the problem statement is well defined and was solved using SIP method as detailed below.

Problem Definition	Problem Statement: There is no agreed concept to bring harmonisation of labelling requirements in the SADC region, despite the current efforts by the AMRHi		
Sub Problems	What are the barriers to labelling harmonisation and how do we overcome them?	Which framework addresses the differences and embraces the similarities?	How to get the SADC stakeholders to agree to a single framework?
Problem Analysis	Comparative analysis of legal requirements and Identification of barriers to harmonisation	A Systemic review of the outcomes of the comparative study and logical proposal of a harmonised framework	Stakeholders assessment of harmonised framework through a prospective survey
Problem analysis method	Qualitative Comparative analysis [See 2.1.1]	Framework development [See 2.1.2]	Prospective survey [See 2.1.3]
Solution Convergence	Assessment of the analysis outcomes above and proposal of a regionally validated concept		
Implementation	Make recommendations to SADC MRH Programme		

2.1.1. Qualitative comparative analysis

A Qualitative comparative analysis was performed of the legal requirements for the control of labelling in selected SADC countries: South Africa, Zimbabwe, Namibia, Botswana and Zambia. The choice of countries considered in this study is discussed in detail in section 2.3. In this comparative analysis, the similarities and differences of the legal provisions between the countries was explored.[48]

The qualitative comparative analysis involved;

Understanding the country level legal landscape by identifying the current laws, regulations and guidelines on labelling in operation in the selected SADC countries and other reference jurisdictions or programs such as the EU. The legal provisions were studied 'on as written basis'.[48] The study did not delve into studying the law governing labelling 'on as applied basis' which considers the application of the law and the cultural context in which the law was applied. This will involve studying practical cases in which the law was implemented and will be considered in future studies as it is a crucial part of comparative law studies.

Head to head comparison of the legal requirements as specified in the current documented legal and regulatory requirements.

For each of the line items under review, the following outcomes were explored;

- *Conflicting requirements* – when there is disharmony or antagonistic requirements from at least one of the countries in comparison to the rest of the countries. This is a significant barrier to harmonisation. A mechanism to resolve such conflicts was being sought in this study.
- *Congruent requirements* – when the requirements across the countries are the same, this means that harmonisation of requirements pre-exists.
- *Unique requirements* – when there is a requirement that is peculiar to one country. This requirement should not conflict with the rest of the other countries' requirements. In such cases adoption of the requirement deemed unique to one country by the other countries will augment the legal standing of the receiving country. Improvement of the local legal framework on the basis of international/regional practice is the end in view of International Comparative Law[49]. The corresponding outcomes as stated above was reported for each line item in the head to head comparison.

2.1.2. Framework Development

The outcome of the comparability study above was used to formulate a harmonisation framework for SADC as illustrated below;

Comparability Study Outcome	Solution
Conflicting requirements – when there is disharmony or antagonistic requirements from at least one of the countries in comparison to the rest of the countries.	The conflicting requirements will be compared to other international bodies (EU). Convergence to a 'middle ground' was recommended.
Congruent requirements – when the requirements across the countries are the same, this means that harmonisation of requirements pre-exists.	No further action required, Rewording in a single document was be required for the relevant line items.
Unique requirements – when there is a requirement that is peculiar to one country.	It was proposed that the unique requirements be adopted by the rest of the countries provided that they are not contrary to any other legal requirements

2.1.3. Stakeholder and Expert assessment & validation

Stakeholders from selected SADC countries and experts in the Regulatory harmonisation fraternity were identified to review the proposed harmonised framework using a prospective survey questionnaire. The data collected using the questionnaire was both quantitative and qualitative. Data collected from the survey was collated and analysed using basic statistical functions.

Design and Piloting of the Questionnaire

The questionnaire for the prospective survey was developed following the results of the comparability analysis and formulation of the harmonised framework. To facilitate data collection, an electronic form was designed as a google form. The objective of the survey was to determine the acceptability of the proposed harmonisation framework. Before the final distribution of the questionnaire, a pilot survey was undertaken to validate and check the effectiveness of the questionnaire. This involved three respondents, one from MCAZ and two independent regulatory consultants. The final questionnaire was adapted based on

comments by the pilot respondents.

Distribution of Questionnaire

As stated above, the questionnaire was developed on an open-source online platform (Google form) and used for ease of delivery and collection of data. The questionnaire was accessible as a web link and could be completed online using checkboxes, dropdown lists as well as text entry for open-ended questions. The web link was sent by email to identified respondents. After one month, a reminder email was sent to the prospective recipients. The cutoff period for acceptance of responses was three months, and data analysis was performed with data available.

2.2. The justification for Method Used

System Improvement Process (SIP) methodology was used as an overarching method for this study. The overall aim of this research was to develop and propose a framework that can be adopted or adapted by SADC for harmonisation. The SIP methodology provides a systemic method of changing the status quo from disharmony to a place of convergence where regulatory alignment concerning labelling can be achieved.

Qualitative comparative analysis was used to document the current regulatory landscape, determine the similarities and differences. Qualitative comparative analysis is a conventional method used in comparative law.

Logical derivation was used to define a harmonised framework. This considered the current landscape and used convergence principles to address the differences identified. Convergence could serve the SADC region better since there are existing systems, making few changes towards convergence of requirements could be more acceptable and more comfortable to implement compared to total changes to the system.

A qualitative prospective survey was used to determine the acceptability of the proposed harmonised framework. The survey allowed stakeholders and experts to review the proposed framework using a structured questionnaire objectively. Open-ended questions were also included in the study to solicit further comments from the experts and stakeholders from the selected countries.

2.3. Inclusion criteria for selected SADC stakeholders:

At the initiation of AMRHi, by NEPAD[50], the NMRAs in SADC were classified as follows;

Criteria	Category 1 (meeting < 3 criteria?)	Category 2 (meeting 3 – 4 criteria)	Category 3 (meeting all five criteria)
1. Existing NDRA 2. Existing legal framework 3. Performance of full regulatory functions 4. Existing Management Information System 5. Available Human Resources	Lesotho, Swaziland, Seychelles, DRC, Angola	Malawi, Mozambique, Zambia, Botswana, Mauritius, and Namibia	South Africa, Tanzania, Zimbabwe

The vast disparities in medicine regulatory capability, as shown above, was found to be a barrier to harmonisation at the outset. Harmonisation initiatives were confounded by other factors such as the sheer size of SADC (15 Countries) and other factors such as language. These confounding factors are the reason for the slow pace of the SADC Medicine Regulatory Harmonisation Project. On this background, SADC adopted the Zazibona as the official project on regulatory harmonisation in SADC. This enabled SADC to form a nucleus of NMRAs whose regulatory capabilities are similar and are small enough to allow dialogue, work sharing and progression towards harmonisation. The countries initially involved in Zazibona were Zambia, Zimbabwe, Botswana and Namibia. At the time of writing, South Africa and DRC had joined as a main member and other SADC countries (Swaziland, and Mozambique) had joined Zazibona as observers. It is anticipated that, with the incorporation of more countries as members, Zazibona will eventually achieve the goal of harmonisation in the SADC region.

On this basis, this research focused on countries participating in Zazibona as the primary stakeholders at the time the proposal was made. Further consultation and engagement with the rest of the SADC countries and industry will be required before finalisation of the harmonised labelling concept. The outcome from the focus on Zazibona participating countries provided a representative blueprint for broader engagement. Over and above the NMRA stakeholders from Zazibona, experts, consultants and office bearers in organisations involved in the AMRHi projects in SADC were also included in the study. The respondents for this study therefore included;

- Technical officer of the AMRHi – SADC MRH (1)

- Expert / Consultant involved in Zazibona (1)
- Technical officer (s) in the WHO Technical assistance program (1)
- NMRA representatives from the selected SADC countries (Zazibona) (5)

2.4. Data collection and analysis

For comparability analysis head to head comparison of the legal and regulatory provisions 'on as written basis' was used. The requirements were obtained from the current acts, regulations and guidelines published in the selected countries. The results were tabulated to show the areas of conflict or congruency.

A Google form based online questionnaire was used to collect data for the stakeholder assessment of the harmonised label. Responses were collated, analysed at the backend using functionalities in google sheets. Google Sheets is fully compatible with Microsoft Excel functions allowing primary statistical analysis to be used in the prospective survey. Data was presented in the form of pie charts and bar graphs. No further manipulation of data was required. Due to limited number of participants, in-depth statistical analysis was not possible. It is recommended that a follow up study targeting all the SADC member states should be performed.

2.5. Ethics

Approval to conduct the study was obtained from the University of the Witwatersrand Human Research Ethics Committee on 28 August 2015. Respondents to the survey participated voluntarily, this was specified as part of terms and conditions on the google form.

2.6. Limitations

The stakeholder assessment could have delved into more detail if other methods were used such as focused group discussions. This would require convening a meeting/workshop with the relevant stakeholders. Resource constraints did not allow this method to be used in this study. Responses were therefore sought through the electronic questionnaire.

3. Comparability analysis of legal requirements

3.1 The Legal and Regulatory Landscape

The table below summarises the legislative provisions and guidelines for labelling of pharmaceuticals. For each country, the relevant act, regulations and guidelines are listed.

Table 2: Summary of the regulatory landscape governing labelling of pharmaceuticals

Country	Act	Regulations	Guideline (s)
South Africa	Medicines and Related Substances Act, 1965 (Act 101 of 1965 as amended); Section 18: Labels and advertisements ▪ Consolidated Schedules as per Section 22A(2)	General Regulations made in terms of the Medicines and Related Substances Act, 1965 (Act 101 of 1965), as amended (2017); ▪ Section 10: Immediate container label ▪ Section 11: Package inserts ▪ Section 12: Patient information leaflet ▪ Section 9: Categories and classification of medicines	▪ Patient information Leaflets ▪ Proprietary names for medicines ▪ Package insert for Human Medicines ▪ Package Insert Standardised text ▪ Labelling of sugars ▪ Scheduling of medicines ▪ International Metric System (SI)
Zimbabwe	Medicines and Allied Substances Control Act [chapter 15:03]; Section 36: Medicines to be labelled	Medicines and Allied Substances Control Act (General) Regulations, 1991. (S.I. 150 of 1991); Sections; Section 37. Labelling and marking of medicines Section 38. Package inserts Section 39. Categories for distribution Schedules; ▪ Fifth Schedule: Pharmacological classification categories of medicines ▪ Sixth Schedule: Categories for the distribution of medicines ▪ Seventh Schedule: Conditions for which advertising prohibited	Guideline on submission of documentation for Registration of a multisource (generic) finished Pharmaceutical product (FPP): quality part in The common technical document (CTD) format; ANNEX III: SMPC/ Package Insert

Country	Act	Regulations	Guideline (s)
		▪ Eighth Schedule: Specially Restricted Preparations (S.R.) ▪ Eighth Schedule: Psychotropic Substances ▪ Ninth Schedule: Prescription Preparations (P.P.) ▪ Tenth Schedule: Prescription Preparations (P.P. 10) ▪ Eleventh Schedule: Pharmacist Initiated Medicines (P.I.M.) ▪ Twelfth Schedule: Pharmacy medicines (P.) and Veterinary Medicines (General Dealer) (V.M.G.D.) ▪ Thirteenth Schedule: Prohibited Medicines (P.M.) ▪ Fourteenth Schedule: Narcotic medicines (N.)	
Zambia	The Medicines and Allied Substances Act, 2013 Sections; **40.** (1) The categories of medicines to which this Part applies **43.** Medicines shall be labelled	Annex I Labelling of medicines based on statutory Instrument no. 47 of 1993 - Labelling of medicines ▪ SI 47 of 1993 only provides for the label information. No information is given for the leaflets	General guidelines for submitting applications for registration of medicines, 5th edition *NB: Guideline above superseded with the CTD guideline. However, the CTD guideline does not provide guidance on labelling.*
Botswana	Drugs and Related Substances Act no. 18 of 1992 PART IV — Miscellaneous *Drugs and Related*	Statutory Instrument No. 46 of 1993 Drugs and Related Substances Act, 1992 (Act no. 18 of 1992) Drugs and Related Substances Regulations, 1993 (Published on 16th April 1993); Section 8: Labels *Regulation to Drugs and Related Substances Act 8, 2013 are not yet promulgated hence the previous regulations are the ones in use*	MH 2048, FORM 1 - Leaflet format *NB: Form above superseded with the CTD form 1.2.1. However, the CTD guideline does not provide guidance on labelling.*

Country	Act	Regulations	Guideline (s)
	Substances Act 8, 2013		
Namibia	Medicines and Related Substances Control Act, 2003 (Act No. 13 of 2003), Section 24: Labels and advertisements	Medicines and Related Substances Control Act, 2003: Regulations relating to Medicines and Related Substances ▪ Section 11: immediate container label ▪ Section 12: Package inserts ▪ Section 13: Patient information leaflet ▪ Annexure I: Pharmacological classification of categorised medicines	No Guideline provided in the CTD regime

In all the participating countries, applicants are instructed to comply with labelling requirements as a condition of registration. These requirements are mandatory legal provisions and must be complied with. In line with national sovereignty and independence, each country demands that its prescribed conditions should be met. A mechanism to assist in the convergence of these requirements was urgently required and hence became the overall aim of this study.

In the review of the legal provisions, it was noted that the information required for labelling was prescribed in either guidelines or regulations and not in the principal act. The principal act in all cases only stated that medicines should be labelled as per regulations or guidelines. It also stated to which products the labelling requirements apply. In all cases, it also provided for the Minister of Health in consultation with the relevant stakeholders to prescribe regulations and guidelines for the labelling.

This is particularly important as the formulation or update of regulations and guidelines follows a much simpler process compared to update or changes to the principal act. Therefore, the opportunity to harmonise or converge the labelling requirements could easily be achieved if the political will is present. Forums already exist such as the SADC Ministers of Health & Head of NMRA agencies meetings in which deliberations and resolutions to converge the regulations and guidelines without prejudice can be made. Once this resolution is made in the SADC structures, individual countries, through the relevant structures for legislative changes may update the relevant regulations and guidelines to reflect the harmonised / convergence position.

3.2 Comparative analysis of the requirements for labelling components:

3.2.1 Comparison of requirements for immediate container labels and cartons:

In this section, a head to head comparison of the requirements for immediate container label / carton as stated in the relevant regulations was performed and tabulated in the table below. For each of the line items under review, the following outcomes were observed as discussed in 2.1.1;

- Conflicting requirements
- Congruent requirements
- Unique requirements.

Refer to table 3 below for a detailed assessment.

Table 3: Comparison of requirements for immediate container labels and cartons

Prescribed Labelling particulars	**South Africa Act 101 of 1965 & Regulations**	**Zimbabwe Act 15:03 & Regulations SI 150 of 1990**	**Namibia Act No. 13 of 2003 & Regulations**	**Botswana Act no. 18 of 1992 & Regulations**	**Zambia Regulations SI 47 of 1993**	**Evaluation Outcome and Recommendations**
Scheduling status / Category of distribution	Yes Regulation 10(1)(a) In a square box, preceding the proprietary name **[S0-S8]**	Yes Regulation 37(1)(l) As per 6th schedule of SI 150 of 1991 **[HR, P, PIM, PP10, PP, DD, etc]** *See table 2 for full list and definition*	Yes Regulation 11(1)(l) In a square box, preceding the proprietary name, **[NS1 – NS5]**	Yes Regulation 8(1)(k) **[S1-S4]**	Yes Regulation (1)(m) **[GS, PS, POM]**	**Conflicting Requirements** Differ between countries. Botswana and South Africa scheduling: the same schedule may apply to different product classes with different risk-benefit ratios. This has huge implications for the rational use of medicines
Registration Number	Yes Regulation 10(1)(c) **Unique No. Issued by MCC**	Yes MASCA 15:03 36(1) **Unique No. Issued by MCAZ**	Yes Regulation 11(1)(b) **Unique No. Issued by NMRC, followed by the expression (Act No.13 of 2003)**	Not specified **Unique No. Issued by DRU**	Yes Regulation (1)(k) **Unique No. Issued by ZAMRA**	**Conflicting Requirements** A unique registration number is given by each country This confirms that the product has been evaluated by the NMRA and registered based on Quality, Safety and Efficacy (QSE) data. The Number is the basis of verification by NMRA and is a unique identifier of the product on the market.
Brand Name	Yes Regulation 10(1)(b)	Optional Regulation 37(1)(c) Should be less prominent than the generic name	Yes Regulation 11(1)(a)	Optional Regulation 8(1)(b)	Yes Regulation (1)(a)	**Conflicting Requirements** Conflicting requirement between countries: For South Africa and Namibia: Brand Name should be more prominent. Whereas Zimbabwe requires the brand name to be more

Prescribed Labelling particulars	South Africa Act 101 of 1965 & Regulations	Zimbabwe Act 15:03 & Regulations SI 150 of 1990	Namibia Act No. 13 of 2003 & Regulations	Botswana Act no. 18 of 1992 & Regulations	Zambia Regulations SI 47 of 1993	Evaluation Outcome and Recommendations
						prominent. Primary unique identifier of the product as termed house mark.
Generic Name	Not Specified	Yes Regulation 37(1)(c) **Generic name more prominent than the brand name (including font size)**	Yes Regulation 11(1)(d) **Adjacent to the brand name** **<u>Lettering</u>:** **(i) FDC >0.5 of the brand font,** **(ii) non-FDC – same as the Brand name**	Yes Regulation 8(1)(a)	Yes Regulation (1)(a)	**Conflicting requirement** between countries: For South Africa and Namibia: Brand Name should be more prominent, whereas Zimbabwe requires the generic name to be more prominent.
House mark / Logo for HCR/Principal/manufacturer	Not Specified	Yes Regulation 37(1)(d) & 37(3) For Principal or manufacturer *Could be Brand Name*	Not specified	Not specified	Not specified	**Unique requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
Dosage form	Yes Regulation 10(1)(d)	Not Specified	Yes Regulation 11(1)(c)	Not specified	Not specified	**Unique requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
Unit composition	Yes Regulation 10(1)(e)	Yes Regulation 37(1)(e)	Yes Regulation 11(1)(d)	Yes Regulation 8(1)(d)	Yes Regulation (1)(c)	**Congruent requirements** Item not specified by the other countries could be included without impacting on rational

Prescribed Labelling particulars	South Africa Act 101 of 1965 & Regulations	Zimbabwe Act 15:03 & Regulations SI 150 of 1990	Namibia Act No. 13 of 2003 & Regulations	Botswana Act no. 18 of 1992 & Regulations	Zambia Regulations SI 47 of 1993	Evaluation Outcome and Recommendations
	For FDC starting with API of highest schedule					use of drugs – may improve the safe use of drugs.
Strength of medicine	Not specified	Yes Regulation 37(1)(j)	Yes Regulation 11(1)(d)	Not specified	Not specified	**Unique requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
% Bacteriostatic	Yes Regulation 10(1)(f)	Yes Regulation 37(1)(f)	Yes Regulation 11(1) (e.)	Not specified	Not specified	**Unique requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
% anti-oxidant	Yes Regulation 10(1)(g)	Not specified	Yes Regulation 11(1)(f)	Not specified	Not specified	**Unique requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
For oral & parenteral:						
- **Quantity of Sugar**	Yes, Regulation 10(1)(h)(i) More details in guideline 2.35 Labelling sugars	Not specified	Not specified	Not specified	Not specified	**Unique requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
- **% Alcohol**	If quantity > 2% w/w Yes Regulation 8(1)(h)(ii)	Not specified	Yes Regulation 11(1)(f)	Not specified	Not specified	**Unique requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the

Prescribed Labelling particulars	South Africa Act 101 of 1965 & Regulations	Zimbabwe Act 15:03 & Regulations SI 150 of 1990	Namibia Act No. 13 of 2003 & Regulations	Botswana Act no. 18 of 1992 & Regulations	Zambia Regulations SI 47 of 1993	Evaluation Outcome and Recommendations
						safe use of drugs.
Pack size	Yes Regulation 10(1)(i)	Yes Regulation 37(1)(i)	Yes Regulation 11(1)(g)	Regulation 8(1)(c)	Not specified	**Congruent Requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
Indications	Yes, where practical Regulation 10(1)(j)	Not specified	Yes Regulation 11(1)(h)	Not specified	Not specified	**Unique requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
Dosage & Directions	Yes, if practical Regulation 10(1)(k)	Yes Regulation 37(1)(m)	Yes Regulation 11(1)(i)	Yes, for non-prescription Regulation 8(1)(j)	Yes Regulation (1)(e)	**Congruent Requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
Instructions: Shake the before use	Yes Regulation 10(1)(l)	Not specified	Yes Regulation 11(1)(j)	Not specified	Not specified	**Unique requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
For Parenteral: Route of administration	Yes - IV, IM, etc. Regulation 10(1)(m)	Not specified	Yes Regulation 11(1)(k)	Not specified	Not specified	**Unique requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
Batch Number	Yes Regulation 8(1)(n)	Yes Regulation 37(1)(h)	Yes Regulation 11(1)(m)	Yes Regulation 8(1)(f)	Yes Regulation (1)(i)	**Congruent Requirements** Item not specified by the other countries could be included

Prescribed Labelling particulars	South Africa Act 101 of 1965 & Regulations	Zimbabwe Act 15:03 & Regulations SI 150 of 1990	Namibia Act No. 13 of 2003 & Regulations	Botswana Act no. 18 of 1992 & Regulations	Zambia Regulations SI 47 of 1993	Evaluation Outcome and Recommendations
						without impacting on rational use of drugs – may improve the safe use of drugs.
Expiry Date	Yes Regulation 10(1)(o)	Yes Regulation 37(1)(g)	Yes Regulation 11(1)(n)	Yes Regulation 8(1)(g)	Yes Regulation (1)(h)	**Congruent Requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may actually improve the safe use of drugs.
Manufacturing date	Yes Regulation 10(2)(b)	Yes Regulation 37(1)(g)	Yes Regulation 11(1)(o)	Not specified	Yes Regulation (1)(j)	**Unique requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
Name and address of HCR or Principal	Yes Regulation 10(1)(p)	Yes Regulation 37(1)(a)	Not Specified	Not specified	Not specified	**Unique requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
Manufacturer Name & address	Yes Regulation 10(2)(a)	Yes Regulation 37(1)(b) Maybe waived Regulation 37(2)	Yes Regulation 11(1)(p)	Yes Regulation 8(1)(e)	Yes Regulation (1)(l)	**Unique requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
Storage conditions	Yes, Regulation 10(1)(q) as per stability guideline	Yes Regulation 37(1)(k)	Yes Regulation 11(1)(q)	Yes, Regulation 8(1)(h) as per stability guideline	Yes Regulation (1)(g)	**Congruent Requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
Statement: For external use only	Yes Regulation	Yes Regulation	Yes Regulation 11(1)(r)	Yes Regulation 8(8)	Not specified	**Congruent Requirements** Item not specified by the other

Prescribed Labelling particulars	South Africa Act 101 of 1965 & Regulations	Zimbabwe Act 15:03 & Regulations SI 150 of 1990	Namibia Act No. 13 of 2003 & Regulations	Botswana Act no. 18 of 1992 & Regulations	Zambia Regulations SI 47 of 1993	Evaluation Outcome and Recommendations
	10(1)(r)	37(1)(m) {Provided for implicitly}				countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
Warning: Keep out of reach of children	Yes Regulation 10(1)(s)	Yes Regulation 37(1)(m) {Provided for implicitly}	Yes Regulation 11(1)(s)	Not specified, but provided for by Regulation 8(1)(i)	Not specified	**Congruent Requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
Aspirin/Paracetamol Containing – Do not use for more than ten days without consulting a doctor	Yes Regulation 8(1)(t)	Yes Regulation 37(1)(m) {Provided for implicitly}	Not specified	Yes Regulation 8(5)(1, 2 & 3)	Not specified	Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
Paracetamol containing: CONTAINS PARACETAMOL	Yes Regulation 8(1)(u)	Yes Regulation 37(1)(m) {Provided for implicitly}	Yes Regulation 11(1)(w)	Yes Regulation 8(5)(3)	Not specified	**Congruent for four countries** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
Aspirin-containing: not for children Under 12 years old	Not specified	Yes Regulation 37(1)(m) {Provided for implicitly}	Yes Regulation 11(1)(x)	Yes Regulation 8(5)(1)	Not specified	**Unique requirements** Item not specified by the other countries could be included without impacting on rational use of drugs
Fluoride-containing – contains fluoride	Yes Regulation 8(1)(u)	Yes Regulation 37(1)(m) {Provided for implicitly}	Not specified	Not specified, but provided for by Regulation 8(1)(i)	Not specified	**Unique requirements** Item not specified by the other countries could be included without impacting on rational use of drugs.
Antihistamine-containing: drowsiness warnings, aggravated by alcohol and	Yes Regulation 10(1)(v)	Yes Regulation 37(1)(m)	Not specified	Yes Regulation 8(5)(5)	Not specified	**Unique requirements** Item not specified by the other countries could be included

Prescribed Labelling particulars	South Africa Act 101 of 1965 & Regulations	Zimbabwe Act 15:03 & Regulations SI 150 of 1990	Namibia Act No. 13 of 2003 & Regulations	Botswana Act no. 18 of 1992 & Regulations	Zambia Regulations SI 47 of 1993	Evaluation Outcome and Recommendations
CNS depressants		{Provided for implicitly}				without impacting on rational use of drugs – may improve the safe use of drugs.
Eye Drops: Do not use >30 days after opening	Yes Regulation 10(1)(w)	Yes Regulation 37(1)(m) {Provided for implicitly}	Yes Regulation 11(1)(t)	Not specified, but provided for by Regulation 8(1)(i)	Not specified	**Unique requirements** Item not specified by the other countries could be included without impacting on rational use of drugs
Tartrazine containing: Contains Tartrazine	Yes Regulation 10(1)(y)	Undesirable substance – As per 15th schedule of SI 150 of 1991	Yes Regulation 11(1)(v)	Not specified, but provided for by Regulation 8(1)(i)	Not specified	**Unique requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
Warning: Do not exceed the stated dose for Pharmacy Drugs except for Prescription preparations	Not specified	Yes Regulation 37(1)(m) {Provided for implicitly}	Not specified	Yes Regulation 8(9)	Not specified	**Unique requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
Any other conditions requested/directed by NMRA but not included in the regulation	Yes Regulation 10(4) *MCC may accept particulars not required regulation 10 (4)*	Yes Regulation 37(1)(o)	Yes Regulation 11(3)(a)	Yes, Regulation 8(1)(k)	Not specified	**Unique requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may actually improve the safe use of drugs.
Any warnings should be in a different colour to the one used for the rest of the label	Not specified	Yes Regulation 37(1)(o)	Yes Regulation 11(1)(u) Different colour not required	Not specified	Not specified	**Unique requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
Quality of Medicine, USP, BP, etc.	Not specified	Not specified	Not specified	Not specified	Yes Regulation (1)(d)	**Unique requirements** Item not specified by the other countries could be included

Prescribed Labelling particulars	South Africa Act 101 of 1965 & Regulations	Zimbabwe Act 15:03 & Regulations SI 150 of 1990	Namibia Act No. 13 of 2003 & Regulations	Botswana Act no. 18 of 1992 & Regulations	Zambia Regulations SI 47 of 1993	Evaluation Outcome and Recommendations
						without impacting on rational use of drugs – may improve the safe use of drugs.
Provision for the inclusion of information that is not listed in the regulations (on request by the applicant or directed by NMRA	Not specified	Not specified	Yes Regulation 11(3)(a)	Not specified	Not specified	**Unique requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.
Provisions for application to deviate from the requirements of the label	Not specified	Yes Regulation 37(2)	Yes Regulation 11(3)(b)	Not specified	Not specified	**Unique requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.

From the head to head comparability assessment above, labelling particulars were classified as congruent or conflicting between countries. Cases where countries had unique requirements were also observed. Barriers to harmonisation existed in the cases where conflicting and unique requirements were observed. Proposals were made to address the barriers and are summarized in the **Evaluation Outcome & Recommendations** column in the table above. These proposals are further discussed in Chapter 4.

3.2.2 Comparison of requirements for Blister labels:

In this table, a head to head comparison of the blister label requirements as stated in the relevant regulations. The purpose of the comparison was to see where the regulations agree, differ or where there are gaps in the requirements by the various countries. Implications if any of the similarities or differences are discussed under the Evaluation Outcome and Recommendations column.

Table 4: Comparison of requirements for Blister labels

Prescribed Labelling particulars	**South Africa Act 101 of 1965 & Regulations**	**Zimbabwe Masca, 15:03 & Regulations**	**Namibia Act No. 13 of 2003 & Regulations**	**Botswana Act no. 18 of 1992 & Regulations**	**Zambia Regulations SI 47 of 1993**	**Evaluation Outcome and Recommendations**
Brand Name	Yes Regulation 8(1)(b)	Optional Regulation 37(1)(c) Brand name hould be less prominent than the generic name	Yes Regulation 11(1)(a)	Optional Regulation 8(1)(b)	Yes Regulation (1)(a)	**Conflicting requirement between countries**: For South Africa and Namibia: Brand Name should be more prominent. Whereas Zimbabwe requires the generic name to be more prominent Primary unique identifier of the product as termed house mark.
Generic Name	Not Specified	Yes Regulation 37(1)(c) **Generic name more prominent than the brand name (including font size)**	Yes Regulation 11(1)(d) **Adjacent to the brand name** **<u>Lettering</u>:** **(iii) FDC >0.5 of the brand font,** **(iv) non-FDC – same as the Brand name**	Yes Regulation 8(1)(a)	Yes Regulation (1)(a)	**Conflicting requirement between countries**: For South Africa and Namibia: Brand Name should be more prominent. Whereas Zimbabwe requires the generic name to be more prominent.

Prescribed Labelling particulars	South Africa Act 101 of 1965 & Regulations	Zimbabwe Masca, 15:03 & Regulations	Namibia Act No. 13 of 2003 & Regulations	Botswana Act no. 18 of 1992 & Regulations	Zambia Regulations SI 47 of 1993	Evaluation Outcome and Recommendations
Batch Number	Yes Regulation 8(1)(n)	Yes Regulation 37(1)(h)	Yes Regulation 11(1)(m)	Yes Regulation 8(1)(f)	Yes Regulation (1)(i)	Congruent requirements
Expiry Date	Yes Regulation 8(1)(o)	Yes Regulation 37(1)(g)	Yes Regulation 11(1)(n)	Yes Regulation 8(1)(g)	Yes Regulation (1)(h)	Congruent requirements
Name and address of HCR or Principal	Yes Regulation 8(1)(p)	Yes Regulation 37(1)(a)	Not Specified	Not specified	Not specified	**Unique Requirements** Item not specified by the other countries could be included without impacting on rational use of drugs – may improve the safe use of drugs.

From the head to head comparability assessment above, labelling particulars were classified as congruent or conflicting between countries. Cases where countries had unique requirements were also observed. Barriers to harmonisation existed in the cases where conflicting and unique requirements were observed. Proposals were made to address the barriers and are summarized in the **Evaluation Outcome & Recommendations** column in the table above. These proposals are further discussed in Chapter 4.

3.2.3 Comparison of requirements for Package Inserts:

Comparison of the Format of Package inserts

In this table, a head to head comparison of the package inserts' requirements as stated in the relevant regulations. The purpose of the comparison is to see where the regulations agree, differ or where there are gaps in the requirements by the various countries. In cases where the requirements are conflicting or unique, a recommendation for convergence is provided in the comments & recommendations column.

Table 5: Comparison of requirements for Package Inserts

South Africa	**Zimbabwe**	**Namibia**	**Zambia**	**Botswana**	**Comments & *Recommendations***
3.1 Scheduling Status Unique as per	9. Category For Distribution	(a) the scheduling status;	9.7 (vii) Restriction on sale /distribution	1) Scheduling status - Allocated by the DAB according to Section 9 of the Act:	Unique for each country as per regulations *The unique scheduling status for each country should be included on the package insert, prefixed by the country name.*
3.3 Proprietary Name And Dosage Form *(proprietary name of medicine is quoted in the body of the leaflet)*	1.. Name Of The Finished Pharmaceutical Product *(generic name of medicine is quoted in the body of the leaflet)*	(b) the proprietary name *(proprietary name of medicine is quoted in the body of the leaflet)*	Proprietary name of a medicinal product Approved generic name(s) *(generic name of medicine is quoted in the body of the leaflet)*	2) Proprietary name and dosage form: *(proprietary name of medicine is quoted in the body of the leaflet)*	Conflicting requirements: *In order to bring harmonisation, when referring to the medicinal product throughout the SmPC text the proprietary name should be used. The generic name should be used when referring to properties of the active substance(s) rather than those of the product*
3.2 Proprietary Name And Dosage Form	3. Pharmaceutical Form	(c) the dosage form;	Dosage form	2) Proprietary name and dosage form: The proprietary name(s) used for different strengths or dosage forms shall be distinguished by at least the corresponding strengths and dosage forms.	Requirements are congruent
3.3 Composition	2. Qualitative And Quantitative Composition	(d) the approved name of each active ingredient and the	Qualitative and quantitative composition	3) Composition: This includes compendial or approved name and quantity	Requirements are congruent

South Africa	Zimbabwe	Namibia	Zambia	Botswana	Comments & *Recommendations*
	B13	quantity thereof, (e) the approved name and quantity of any bacteriostatic or bactericidal agent		per dosage unit (suitable mass or volume) of active and inactive ingredient(s). Excipients shown on the package insert may be listed without specifying quantities.	
3.4 Pharmacological Classification	See 5.1	(h) the category and pharmacological classification as contemplated in regulation 2 and Annexure I to these regulations, respectively;		4) Pharmacological classification: The classification according to ATC groupings as discussed under "Medicine details".	Unique for each country as per regulations *The unique pharmacological classification for each country should be included on the package insert, prefixed by the country's name.*
3.5 Pharmacological Action	5. Pharmacological Properties	(i) the pharmacological action;	9.6 Pharmacological properties	5) Pharmacological and mechanism of action: A brief description of the pharmacological actions and pharmacokinetics of the drug shall be mentioned.	Requirements are congruent
3.5.1 Pharmacodynamic properties	5.1 Pharmacodynamic properties Pharmacodynamic effects *Pharmacological Classification: {see SI 150 of 1991}* *Mechanism of action* *Microbiology (when applicable) Drug resistance (when applicable)* *Cross-resistance (when applicable)*	(j) the pharmacokinetic and Pharmacodynamic properties;	(i) Pharmacodynamic properties - the mode of action of the active ingredient	5) Pharmacological and mechanism of action: A brief description of the pharmacological actions and pharmacokinetics of the drug shall be mentioned.	Requirements are congruent
3.5.2 Pharmacokinetic properties	5.2 Pharmacokinetic properties	(j) the pharmacokinetic and pharmacodynamic	(ii) Pharmacokinetic properties - the absorption, distribution and excretion	5) Pharmacological and mechanism of action: A brief description of the	Requirements are congruent

South Africa	Zimbabwe	Namibia	Zambia	Botswana	Comments & *Recommendations*
		properties;	of the active ingredients should be discussed in detail.	pharmacological actions and pharmacokinetics of the drug shall be mentioned.	
3.5.3 Summary of clinical studies	5.3 Preclinical safety data		(iii) Preclinical safety data - summaries of studies done in animals to indicate the safety of the active ingredient(s) in humans should be included.		Requirements are congruent; where not specified information may be included without conflicting with regulations or guidelines
	4. Clinical particulars		9.5 Clinical particulars		
3.6 Indications	4.1 Therapeutic indications	(k) the indications as approved by the Council	(i) Therapeutic indication(s) - the conditions for which the product is to be used as a medicine should be indicated.	6) Indications: Indications for the drug is applied for shall be supported by appropriate clinical information given under "PHARMACOLOGICAL AND CLINICAL DOCUMENTATION (Page 6 of 7)".	Requirements are congruent
3.7 Contraindications	4.3 Contraindications	(l) the contra-indications;	(iii) Contra-indications- the situations in which the product should not be used are to be stated	7) Contraindications: Both absolute and relative contraindications shall be mentioned.	Requirements are congruent
3.8 Warnings And Special Precautions	4.4 Special warnings and special precautions for use	(p) the side-effects of, and special precautions;	(iv) Special warnings and precautions for use - the situations for which special attention and care should be exercised in the use of the product should be stated	8) Warnings: Warnings should include any applicable statutory label in Regulation 8 (5). All forms of contraceptives, except condoms, shall bear the following warning statement: "This product helps prevent unplanned pregnancy if used properly. It does NOT prevent the transmission of the human immunodeficiency virus (HIV) or sexually transmitted diseases (STD). A condom must be used to prevent HIV	Requirements are congruent

South Africa	Zimbabwe	Namibia	Zambia	Botswana	Comments & *Recommendations*
				or STD transmission." Child warnings should be indicated where applicable. 11) Special precautions necessary for the safe use of the drug shall be mentioned.	
3.9 Interactions	4.5 Interaction with other FPPs and other forms of interaction	(m) the interaction with other drugs	(v) Interactions - all the known and possible interactions that may occur in the use of the product are to be indicated	12) Drug Interactions	Requirements are congruent
3.10 Pregnancy And Lactation	4.6 Pregnancy and lactation	(n) use during pregnancy and lactation;	(vi) Pregnancy and lactation -		Requirements are congruent; where not specified information may be included without conflicting with regulations or guidelines
3.10.1 Pregnancy	4.6 Pregnancy and lactation	(n) use during pregnancy and lactation;	(vi) Pregnancy and lactation - information should be given as to the suitability of the use of the product during pregnancy and lactation		Requirements are congruent; where not specified information may be included without conflicting with regulations or guidelines
3.10.2 Women of Childbearing Potential	-				Unique for South Africa, inclusion by other countries does not conflict with regulations or guidelines
3.10.3 Lactation	4.6 Pregnancy and lactation	(n) use during pregnancy and lactation;	(vi) Pregnancy and lactation - information should be given as to the suitability of the use of the product during pregnancy and lactation		Requirements are congruent; where not specified information may be included without conflicting with regulations or guidelines
3.10.4 Fertility	-				Unique for South Africa, inclusion by other countries does not conflict with regulations or guidelines
	4.7 Effects on ability to drive and use machines		(vii) Effects on the ability to drive and operate		Unique for Zimbabwe and Zambia, inclusion by other

South Africa	Zimbabwe	Namibia	Zambia	Botswana	Comments & *Recommendations*
			machinery - any effects on the ability to drive and operate machinery should be stated		countries does not conflict with regulations or guidelines
3.11 Dosage And Directions For Use	4.2 Posology and method of administration	o) the dosage and directions for use;	9.5 (ii) Route of administration - the instructions for the administration of the medicine should be indicated e.g. for oral use, for external use only, for ophthalmic use etc.	9) Dosage and directions for use: Dosage and directions for use should take into account the use of the drug in special groups like elderly and children and disorders like impaired renal and/or hepatic function, asthma, diabetes, heart disease, etc. Child dosages should be indicated where applicable.	Requirements are congruent
3.12 Side Effects	4.8 Undesirable effects	(p) the side-effects of, and special precautions;	(viii) Undesirable effects - any potential or known undesirable effects associated with the use of the product should be indicated	10) Side effects and special precautions: Side effects should be mentioned by order of occurrence.	Requirements are congruent
3.13 Known Symptoms Of Overdosage And Particulars Of Its Treatment	4.9 Overdose	(q) the known symptoms of overdosage and particulars of its treatment;	(ix) Overdose - the particulars concerning the use of an excessive dose, the effects of this and its treatment should be indicated	13) Known symptoms of over-dosage and particulars of treatment: Signs and symptoms of over-dosage and recommended treatment must be mentioned.	Requirements are congruent
	6. Pharmaceutical particulars		9.7Pharmaceutical particulars		Requirements are congruent
See 3.3	6.1 List of excipients		(i) List of excipients - the common name of the excipients should be used in listing the excipients		Unique for South Africa, Zimbabwe and Zambia, inclusion by other countries does not conflict with regulations or guidelines
-	6.2 Incompatibilities		(ii) Incompatibilities - the incompatibilities of the excipients with each other, the active ingredient(s) and		Unique for Zimbabwe and Zambia, inclusion by other countries does not conflict with regulations or guidelines

South Africa	Zimbabwe	Namibia	Zambia	Botswana	Comments & *Recommendations*
			with the primary packaging		
-	6.3 Shelf life		(iii) Shelf-life - the shelf life of the product in the original unopened container and after reconstitution (where appropriate) should be indicated		Unique for Zimbabwe and Zambia, inclusion by other countries does not conflict with regulations or guidelines
3.14 Identification	See 3.0	s) the identification;		15) Identification: The physical appearance and characteristics of the drug shall be described.	Requirements are congruent; where not specified information may be included without conflicting with regulations or guidelines
3.15 Presentation	6.5 Nature and contents of the container	(t) the presentation;	(v) Nature and composition of containers - the composition of the container and its properties should be indicated especially in respect of the protection of the product	16) Presentation: All types of packaging and pack sizes shall be mentioned.	Requirements are congruent
-	6.6 Instructions for use and handling <and disposal>		(vi) Instruction for use/handling - the instructions for the appropriate use of the product should be indicated Any special features to be carefully observed should be indicated		Unique for Zimbabwe and Zambia, inclusion by other countries does not conflict with regulations or guidelines
3.16 Storage Instructions	6.4 Special precautions for storage	(u) the storage directions,	(iv) Special precautions for storage - the storage instructions should be indicated in terms of temperature and exposure to light should be indicated	17) Storage instructions: Conditions should quote a suitable temperature or temperature range in degree Celsius. Refer to "GUIDELINES FOR STABILITY TESTING".	Requirements are congruent
			9.8 Administrative data		

South Africa	Zimbabwe	Namibia	Zambia	Botswana	Comments & *Recommendations*
3.17 Registration Number	8. Registration Number	(w) the registration number -	(ii) Registration number. The registration number of the product as issued by the PRA should be indicated	18) Registration number: The number allocated by the DAB.	Unique for each country as per register of medicines at the NMRA *The unique Registration Number for each country should be included on the package insert, prefixed by the country's name.*
Not Part of the labelling, Information is placed on the registration certificate			(iii) Date of first registration/renewal of a Product licence. The date when the product was approved / when the registration was renewed should be indicated		Unique for Zambia, inclusion by other countries does not conflict with regulations or guidelines
Regulation 11(7)(a), The name and address of the manufacturer of the medicine;	7.1 Name And Address Of Manufacturer	(x) the name and business address of the manufacturer,			Unique for South Africa, Zimbabwe and Namibia, inclusion by other countries does not conflict with regulations or guidelines
3.18 Name And Business Address Of The Holder Of The Certificate Of Registration	7.2 Name And Address Of Principal	(x) the name and business address of the Holder of such certificate;	(i) Name and address of the holder of a Product licence. The name and address (business and postal) of the Product licence holder should be indicated	19) Applicant: Name and addresses of the applicant must be submitted	Requirements are congruent
3.19 Date Of Publication Of The Package Insert	10. Date Of Publication Of This Package Insert	(y) The date of publication of the package insert.	(iv) Date of (partial) revision of the text. The date when the revised text was approved by the PRA should be indicated	20) Date of publication: Date of approval of the package insert by the DAB.	Requirements are congruent
Regulation 11(7)(a), the scheduling status and registration number allocated by another national medicine regulatory authority of a country as determined by	Regulation 38 (y) any other particulars or warning notices as may be directed by the Authority.	Regulation 12 (2)(b) the inclusion on a package insert of any specified information which is not required by this regulation to be so included; and	9.9 Registration in a SADC member state		Requirements are congruent; where not specified information may be included without conflicting with regulations or guidelines *As per the above*

South Africa	Zimbabwe	Namibia	Zambia	Botswana	Comments & *Recommendations*
the Authority: Provided that this information is surrounded by a square border including the name of the reference country.					*recommendations, the registration details of all the countries in question should be included.*
				14) Conditions of registration: These include sales category, public advertising status, distribution restrictions, etc., as may be decided by the DAB.	Requirements are Unique to Botswana *However the same requirements are included on registration letters, certificates issued by the rest of the SADC NMRAs. We recommend that this requirement is excluded from the labelling but should be maintained in the medicine register, registration certificate or letter of registration.*

From the head to head comparability assessment above, labelling particulars were classified as congruent or conflicting between countries. Cases where countries had unique requirements were also observed. Barriers to harmonisation existed in the cases where conflicting and unique requirements were observed. Proposals were made to address the barriers and are summarized in the comments & recommendations column in the table above. These proposals are further discussed in Chapter 4.

The content of the package insert

In the assessment above, it was seen that the format of the package insert was predominantly congruent. Where unique formatting requirements exist, adoption by other countries could quickly bring the necessary requirements into congruency.

In the assessment of guidelines and requirements for content, it was also observed that differences in the reference guidelines on the content of the package inserts resulted in barriers to harmonisation of package inserts. The table below provides the accepted references used in the compilation of package inserts in the different countries

Table 6: Accepted references for package insert content

	Reference Package Insert		**Additional Guidance / references**
	For Multisource products	For Innovator Products	
South Africa	South African Innovator package insert	International Innovator as approved by a SRA	SAHPRA Guideline on; ▪ Patient information Leaflets ▪ Proprietary names for medicines ▪ Package insert for Human Medicines ▪ Package Insert Standardised text ▪ Labelling of sugars ▪ Scheduling of medicines International Metric System (SI)
Botswana	International Innovator as registered by SRA	International Innovator as registered by a SRA	No additional guidelines provided
Namibia	International Innovator as registered by SRA	International Innovator as approved by a SRA	No additional guidelines provided
Zimbabwe	International Innovator as registered by SRA	International Innovator as approved by a SRA	Guideline on submission of documentation for Registration of a multisource (generic) finished Pharmaceutical product (FPP): quality part in The common technical document (CTD) format; ANNEX III: SMPC/ Package Insert
Zambia	International Innovator as registered by SRA	International Innovator as approved by a SRA	General guidelines for submitting applications for registration of medicines, 5th edition *NB: Guideline above superseded with the CTD guideline. However, the CTD guideline does not provide guidelines on labelling.*

Differences in the acceptable references for package inserts in SADC resulted in differences in the content of the package insert for the same product.

- For multisource products in South Africa, the South African innovator product is regarded as the primary reference whereas for other jurisdiction, the international innovator product is the acceptable reference. In cases where the critical information in the South African Innovator product differs to the information in the International Innovator product e.g. when some indications are approved by the SRA but not SAHPRA or *vice versa*, harmonisation of the leaflet becomes problematic.
- South Africa has extensive guidelines and standard texts for specific sections of the package insert. These guidelines are unique to South Africa but may be adopted by other countries without bringing conflict with statutory requirements.

In order to facilitate harmonisation, the following is recommended,

- The SADC member states should adopt the same package insert (approved by a SRA) as the acceptable reference. All Package insert compilations should follow this approved reference package insert.
- The SADC member states should consider the guidelines that have been implemented in the region by individual member states and converge to the same or similar requirement. Such guidelines include the following guidelines implemented by SAHPRA;
  - 2.20_PI_standardised_texts_Jun15_v4
  - 2.35_Labelling_sugars_Nov15_v1

3.2.4 Assessment of scheduling requirements

Scheduling allows for different levels of regulatory control over pharmacologically active substances, whether in the form of active pharmaceutical ingredients, naturally-occurring products or extracts thereof, or finished pharmaceutical products (medicines). The primary consideration in scheduling a substance is its safety profile, in relation to the therapeutic indications for its use. The categorisation hence controls how patients access medicines in the interest of rational use of drugs. The categorisation in the SADC countries is unique to each country. This is summarized below.

Table 7: Summary - Comparison of Schedules/categories of distribution

South Africa	Botswana	Namibia	Zimbabwe	Zambia
Regulations to Act 101 of 1965 as amended (Regulation 9)	Regulations to Act no. 18 of 1992 (Regulation 20)	Regulations to Act No. 13 of 2003 (Annex 1)	Medicines and Allied Substances Control (General) Regulations, 1991. (S.I. 150 of 1991); SI	Labelling Of Medicines (SI No. 47 OF 1993) 1(m)
Schedule 0 (S0)	Schedule 4 (S4)	Namibian Schedule 0 (NS0)	Household remedy	General Sales
Schedule 1 (S1)	Schedule 3 (S3)	Namibian Schedule 1 (NS1)	Pharmacy Drug Only	Pharmacy Sale
Schedule 2 (S2)	Schedule 3 (S3)	Namibian Schedule 1 (NS1)	Pharmacist Initiated Medicine	Pharmacy Sale
Schedule 3 (S3)	Schedule 2 (S2)	Namibian Schedule 2 (NS2)	Prescription Preparation (PP) / Prescription Preparation in the 10th Schedule (PP10)	Prescription Only Medicine
Schedule 4 (S4)	Schedule 2 (S2)	Namibian Schedule 3 (NS3)	Prescription Preparation (PP / Narcotic (N)	Prescription Only Medicine
Schedule 5 (S5)	Schedule 1D (S1D)	Namibian Schedule 4 (NS4)	Prescription Preparation (PP / Narcotic (N)	Prescription Only Medicine
Schedule 6 (S6)	Schedule 1C (S1C)	Namibian Schedule 5 (NS5)	Specially restricted (SR)	-
Schedule 7 (S7)	Schedule 1B (S1B)	Namibian Schedule 5 (NS5)	Specially restricted (SR) / Prohibited Drug (PD)	-

A quick assessment of the above shows that the categories/schedules for Zimbabwe, Zambia and Namibia are unique to each country. The problem arises with Botswana and South Africa where the same lettering may be applied to medicines in different schedules. For instance, S4 in Botswana stands for medicines that are found in the front shop equivalent to South African S0. This may confuse patients and health professionals if the two are not clearly identified on the

pack. The harmonised labelling should ensure that the lettering for scheduling status can be distinguished from each other. **This can be achieved by prefixing the scheduling status with the country name.**

4. Proposal for the harmonised labelling

The comparative assessment in Chapter 3 showed that the requirements for labelling were either congruent, unique or conflicting. The harmonisation proposal in this chapter was based on these three possible outcomes.

In the case where the requirements are **congruent**, harmonisation pre-exists and no additional changes were required.

However where **unique** requirements were exhibited, two independent actions were required;

a. Where requirements are specific to the country, and each country has its own set of requirements which are not exchangeable with any other countries, the labelling should reflect requirements from each country. For instance, each country will issue a unique registration number at the point of registration of any product. In such cases, convergence was achieved by allowing the registration numbers from all countries on the product labelling preceded with the country's name.

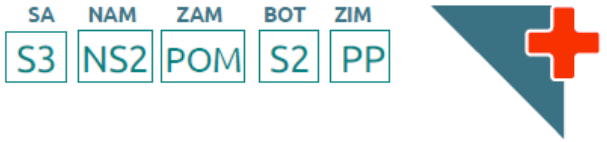
b. Where requirements are specified by one or more country, where the same requirement is omitted by the other country provided that the requirement is not conflicting with any other particular for labelling, the requirement may be adopted by the country which had not specified the same at inception.

Where **conflicting** requirements existed, convergence was achieved by resolving the conflicting provisions. This involved proposing changes to the relevant legal or regulatory provision, see the following sections. Where relevant, reference to recognized regulatory authorities was used e.g. the EU regulations and guidelines. The harmonised framework for labels is discussed in chapter **4.1** and for package inserts in chapter **4.2.**

4.1. The harmonised label concept

The table below summarises the proposal for a harmonised label based on the selected SADC countries represented in this study.

Table 8: Description & Discussion of the harmonised label concept: Label

Particulars	Concept to allow for harmonisation	Illustration - for example
Conflicting requirements		
Proprietary Name and Generic Name	To address the conflicting requirements; It is proposed that the Generic Name (International Non-proprietary name) be presented on the label with the same/similar font size and prominence as the brand name (Proprietary name)	**Proprietary Name** **Active Ingredient 1 X mg,** **Active Ingredient 2 Y mg** This is illustrated in the prototypes given in chapter 4.2
Unique Requirements (a)		
Scheduling status	It is proposed that the scheduling status of all the countries be presented on at least the front panel of the label. To differentiate between the scheduling statuses of the countries, the scheduling status in a square border will be preceded by the country name.	 This is illustrated in the prototypes given in chapter 4.2
Registration Number	Each country issues a registration number as the product is entered into a register. To enable labelling harmonisation, it is proposed that a pane with all the registration details is set up on the label. The registration number will be preceded by the Country name and scheduling status.	 This is illustrated in the prototypes given in chapter 4.2
Unique Requirements (b)		
Various provisions	For any requirement that is not specified by any other country, we propose that it should be included in the	*N/A*

Particulars	Concept to allow for harmonisation	Illustration - for example
	labelling provided that it is value adding and is not conflicting with the country-specific requirements.	
Congruent requirements		
Various Provisions	These do not require further manipulation. The provisions from all countries were found to similar. No Further action was required.	*N/A*

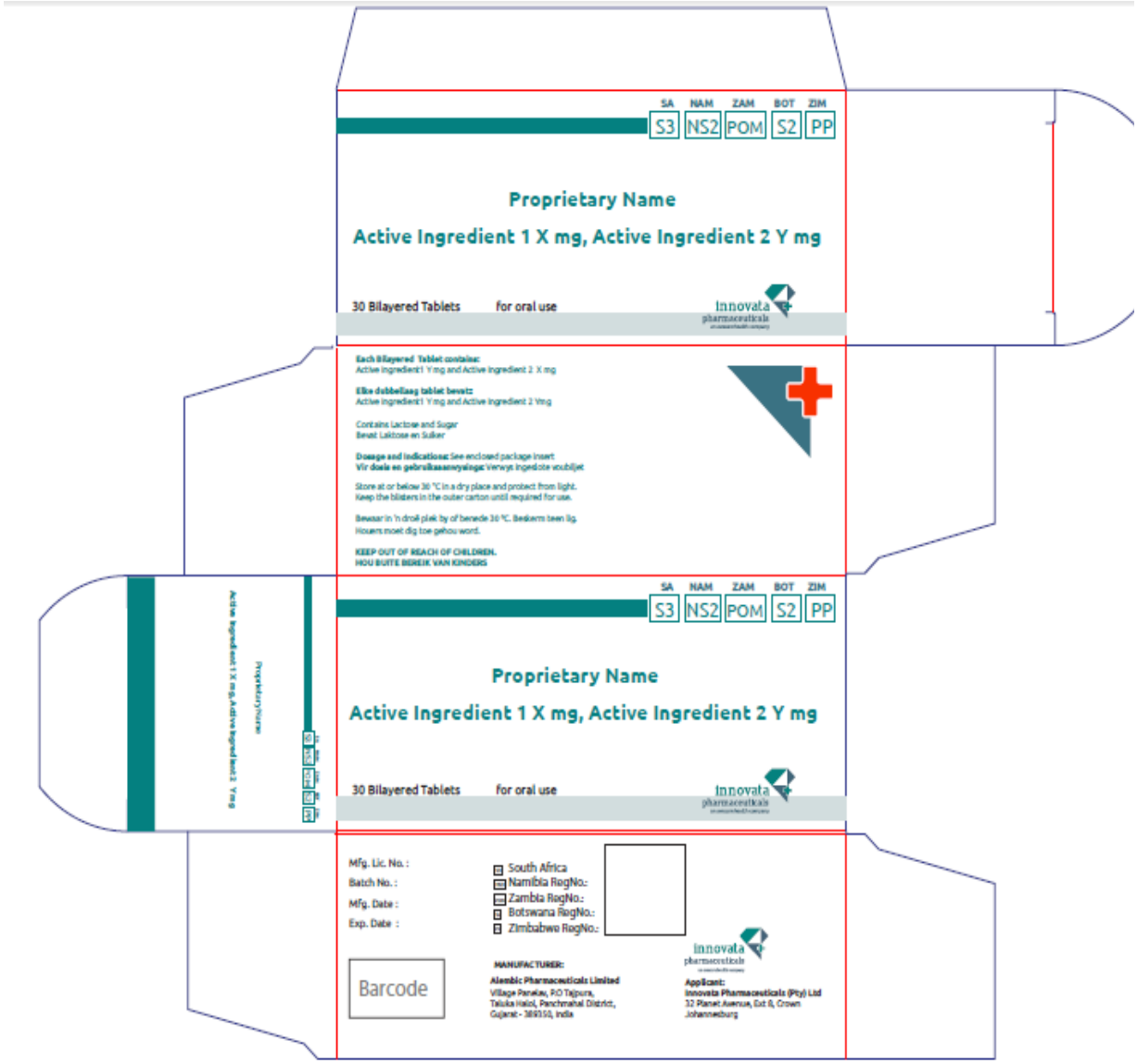
The above proposal is illustrated with dummy label prototypes giving a visual representation of the proposed harmonised label for ease of reference.

4.1.1. Prototypes of the label(s): Immediate container label prototype

Figure 4: Immediate container label prototype

The above is proposed as a template for the immediate container to be used for bulk packs, bottles, etc.

4.1.2. Prototypes of the label(s): Carton prototype – version **1**



The above is proposed as a template for cartons used for blister packs, strip packs and related packaging materials

Figure 5: Carton prototype – version 1

4.1.3. Prototypes of the label(s): Carton prototype – version 2

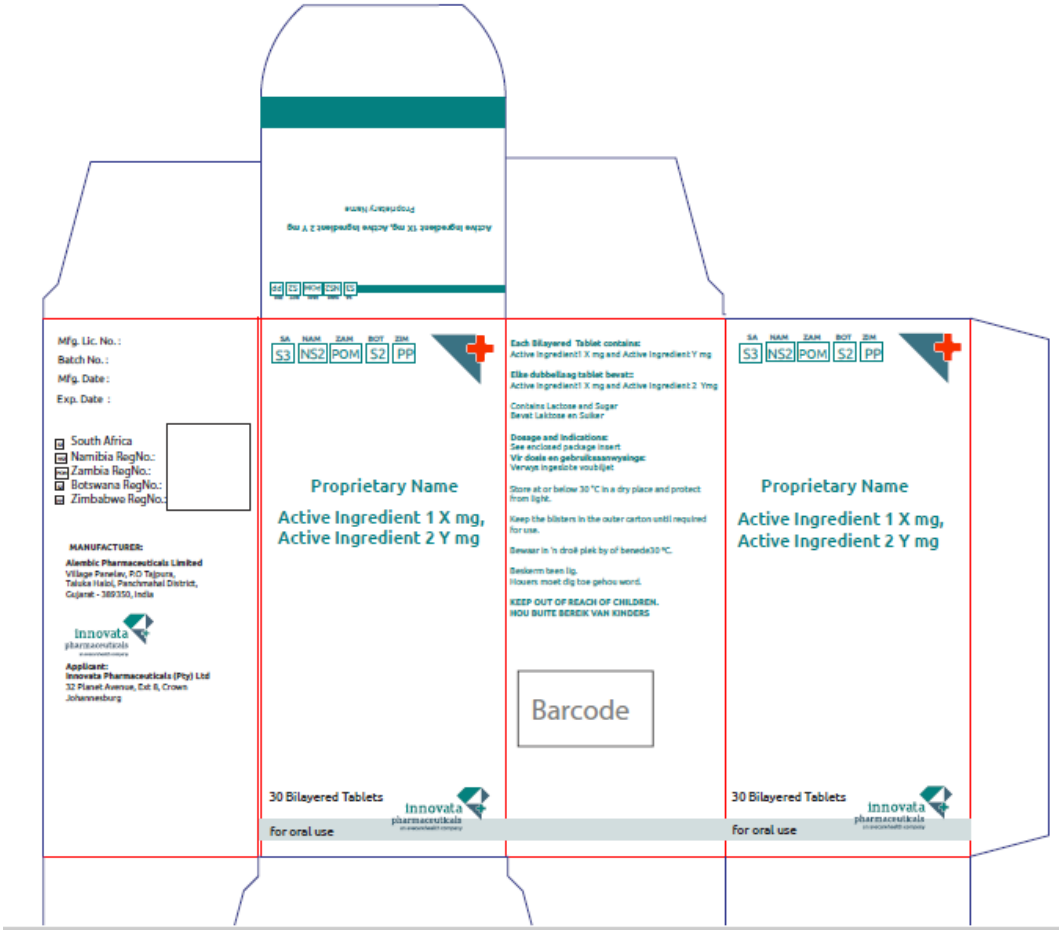


Figure 6: Carton – Version 2 prototype

This carton is proposed as a template for bottles, jars and some blister packs

4.1.4. Prototypes of the label(s): Other Labels:

Figure 7: Blister Label prototype

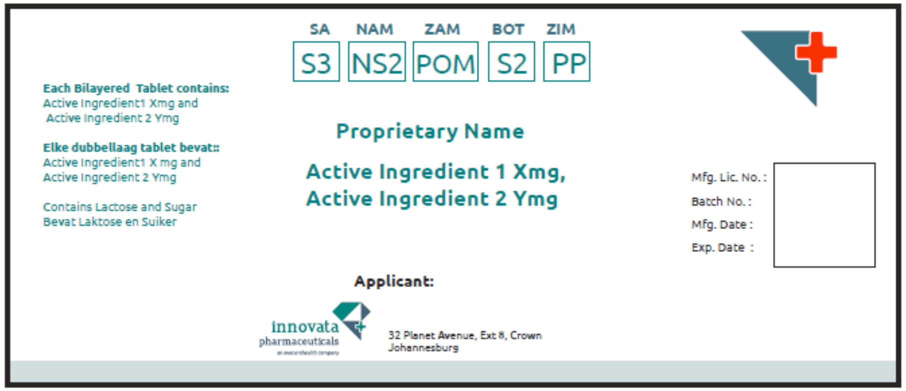


Figure 8: Semisolids (<5g) label prototype

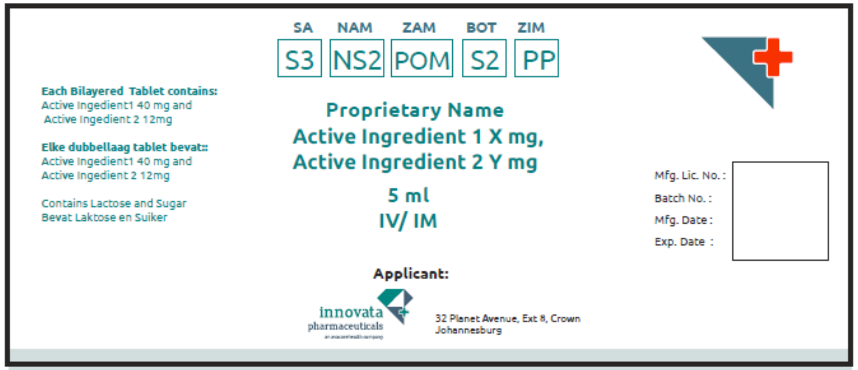


Figure 9: Vials / Ampoules (<5ml) prototype

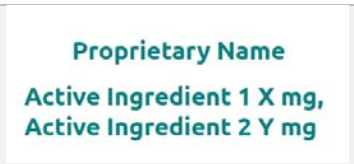
4.2. The Harmonized Package insert concept

Head to head comparative analysis was done and is detailed in Table 5. The assessment showed that while the arrangement of the sections was different from country to country, the actual requirements for each section are comparable. The majority of the sections were found to be congruent between the participating countries.

4.2.1. Harmonising conflicting and unique requirements

A few sections were however either conflicting or unique, these are summarized below. The table below also gives recommendations on dismantling the barriers of harmonisation of Package Inserts.

Table 9 Description of harmonised Package inserts

Particulars	Recommendations	Illustration
Conflicting & Unique (a) requirements		
Scheduling Status / Category of distribution	The scheduling status is unique for each country as per regulations. Schedules for Botswana and South Africa were found to be conflicting as discussed above. The unique scheduling status for each country should be included on the package insert, prefixed by the country name. This is essential in this context to differentiate South African schedules from Botswana schedules.	
Proprietary Name and Generic Name	To address the conflicting requirements, it is proposed that the Generic Name (International Non-proprietary name) be presented on the package insert with the same/similar font size and prominence as the brand name (Proprietary name).	
Name(s) of medicine as quoted in the body of the leaflet	When referring to the medicinal product throughout the SmPC text, the proprietary name should be used. The generic name should be used when referring to properties of the active substance(s) rather than those of the	None

Particulars	Recommendations	Illustration
	product. Currently, some countries require the generic name in the body of the text whereas other countries expect the brand name to be used.	
Pharmacological Classification	The unique pharmacological classification for each country should be included on the package insert, prefixed by the country's name.	*Pharmacological Classification:* **Pharmacological Class – Botswana, South Africa, Zambia, Zimbabwe, -**
Registration Number	The unique Registration Number for each country should be included on the package insert, prefixed by the country's name.	
Registration details of other countries	As per the above recommendations, the registration details of all the countries in question should be included	As above
Unique (b) requirements		
Various	For any requirement that is not specified by any other country, we propose that it should be included in the labelling provided that it is value adding and is not conflicting with the country-specific requirements. These are however the minority for package inserts.	None
Congruent requirements		
Various	These do not require further manipulation. The provisions from all countries were found to similar. No Further action was required.	None

4.2.2. Harmonising the structure of the Package insert

It has already been stated that while the arrangement of package insert / SMPC sections was different from country to country, the actual requirements for each section were comparable. On that note, an aggregable arrangement or format was required in order to converge into this harmonised structure. It is proposed that the format from a region which has successfully harmonised labelling should be adopted. In this case, the European Union's format should be adopted in a similar way as the adoption of scientific guidelines from ICH. The EU Package insert / SMPC format is comparable to most of the SADC sub-region and hence was recommended. The proposed package insert / SMPC structure is given below (Table 10). The EU format coupled with the recommendations in chapter 4.2.2 above could result in acceptable convergence.

Table 10: Format for the proposed harmonised leaflet

Harmonised Package leaflet based on the EU format.
Category for Distribution / Scheduling status 
1. Name of The Finished Pharmaceutical Product <Trade Name> <Generic Name> **Proprietary Name** **Active Ingredient 1 X mg,** **Active Ingredient 2 Y mg**
2. Qualitative and Quantitative Composition
3. Pharmaceutical Form
4. Clinical particulars
4.1 Therapeutic indications
4.2 Posology and method of administration
4.3 Contraindications
4.4 Special warnings and special precautions for use
4.5 Interaction with other FPPs and other forms of interaction
4.6 Pregnancy and lactation
4.7 Effects on ability to drive and use machines
4.8 Undesirable effects
4.9 Overdose
5. Pharmacological Properties

Harmonised Package leaflet based on the EU format.
5.1 Pharmacodynamic properties Pharmacodynamic effects *Pharmacological Classification:* Namibia, Pharmacological Class – Botswana, Pharmacological Class – South Africa, Pharmacological Class – Zambia, Pharmacological Class – Zimbabwe, Pharmacological Class -
5.2 Pharmacokinetic properties
5.3 Preclinical safety data
6. Pharmaceutical particulars
6.1 List of excipients
6.2 Incompatibilities
6.3 Shelf life
6.4 Special precautions for storage
6.5 Nature and contents of container
6.6 Instructions for use and handling <and disposal>
7.1 Name and Address of Manufacturer
7.2 Name and Address of Principal
8. Registration Number
S3 South Africa NS3 Namibia RegNo.: POM Zambia RegNo.: S2 Botswana RegNo.: PP Zimbabwe RegNo.:
10. Date of Publication of This Package Insert

4.2.3. Harmonisation of the content of the package insert

In chapter 3.2.3, the differences in the acceptable references were highlighted as a barrier to the harmonisation of Package Insert / SMPCs. To facilitate harmonisation, the following is recommended,

- The SADC member states should adopt the same package insert – *an international innovator package insert* as the acceptable reference. All Package insert compilations should follow this approved reference package insert.
- The SADC member states should consider the guidelines that have been implemented in the region by individual member states and converge to the same or similar requirement. Such guidelines include the following guidelines implemented by SAHPRA;
  - 2.20_PI_standardised_texts_Jun15_v4
  - 2.35_Labelling_sugars_Nov15_v1

4.2.4. Lifecycle management to the content of the package insert / SMPC

Medicine safety is right at the core of the NMRA's reason for existence. New data is accumulated every day through post-marketing surveillance and pharmacovigilance exercises. It was observed that only one of the countries under study had explicit guidelines to manage safety information updates. Although provided for in the laws of the selected member states, there was no guidance on the management of new safety data which may warrant updating of package inserts. To ensure harmonisation during the product lifecycle, similar guidelines and enforcement structures are required in the participating countries. It is recommended that SADC member states consider international guidelines on safety updates

5. Stakeholder assessment of the harmonised labelling concept

Following a detailed comparative analysis in chapter 3, a harmonisation labelling concept was proposed in chapter 4. In line with the objective of developing a harmonisation framework that is acceptable in SADC, the harmonised labelling concept proposed in chapter 4 was assessed by experts and stakeholders in selected SADC countries. The assessment was done through a prospective online survey using a predesigned questionnaire developed on the Google form platform. This section details the outcome of this assessment. Acceptance by the stakeholders and experts validates the proposed harmonisation framework.

In this study, stakeholders from NMRAs (Zambia, Zimbabwe, Namibia, Batswana, and South Africa), AU (NEPAD) and WHO as well consultants in SADC were invited to participate in the study. Responses (6 of 8 (75%)) were received from all target NMRAs as well as from an independent Zazibona consultant. The countries represented in the study are shown in figure 10 below.

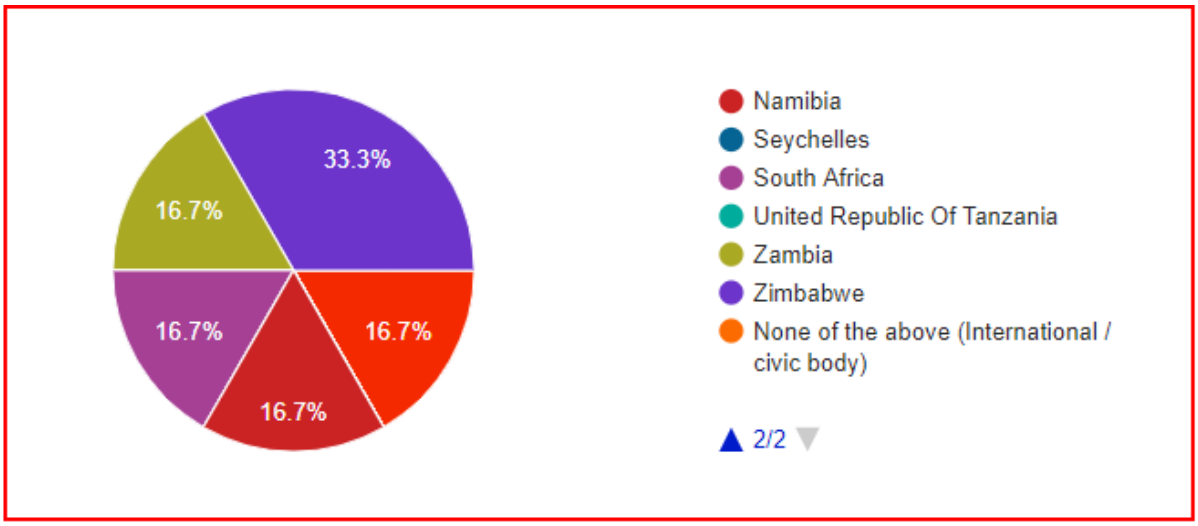


Figure 10: Countries represented in the study

Respondents were mainly Senior Regulatory officers (figure 11) authorised by the head of the respective agency. Hence the responses provided reflect the current thinking within the regulatory authority.

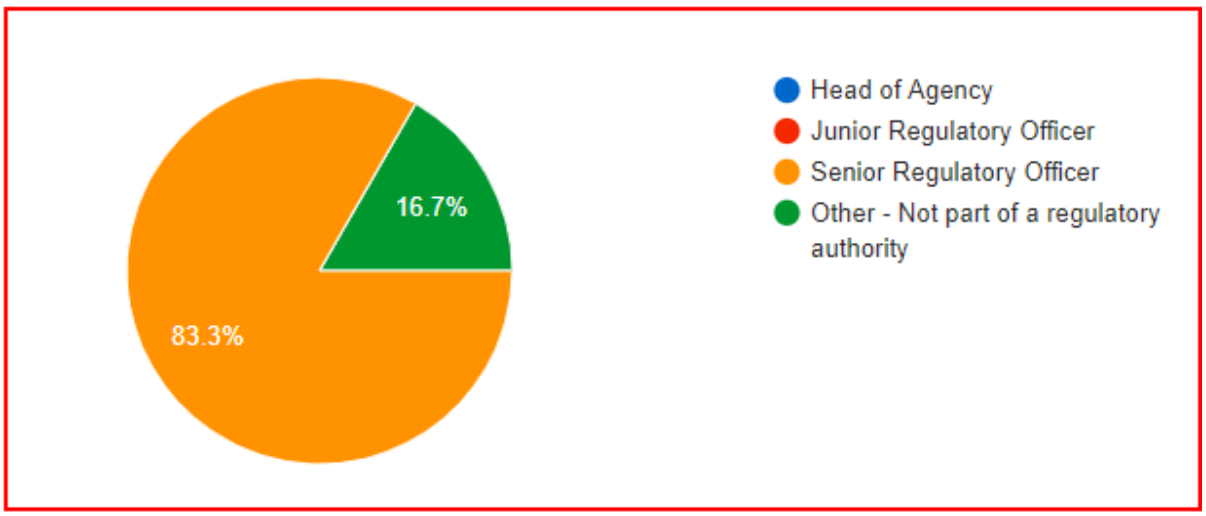


Figure 11: Role of respondents in the NMRA

One respondent declared independence from any of the targeted regulatory authority but is heavily involved in the Zazibona project as a consultant.

5.1. Acceptance of the label harmonisation framework

The various facets of harmonisation were assessed by the stakeholders. All the respondents (100 %) accepted the mechanism below (product naming convention) to facilitate convergence:

Proprietary Name and Generic Name	Generic Name (International Non-proprietary name) shall be presented on the label with the same/similar font size and prominence as the brand name (Proprietary name)	**Proprietary Name** **Active Ingredient 1 X mg, Active Ingredient 2 Y mg**

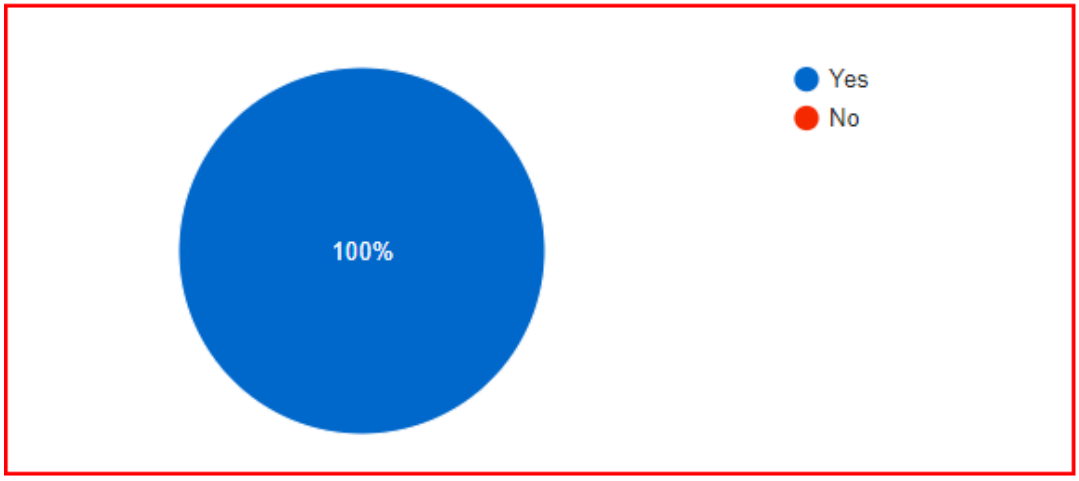


Figure 12: Acceptability of naming convention on labelling

In the same vein, all respondents (83.3 %) accepted the proposed mechanism (position and identification of schedules) to facilitate convergence:

Scheduling status	The scheduling status of all the countries shall be presented on at least the front panel of the label. To differentiate between the scheduling statuses of the countries, the scheduling status in a square border is preceded by the country name.	SA NAM ZAM BOT ZIM S3 NS2 POM S2 PP

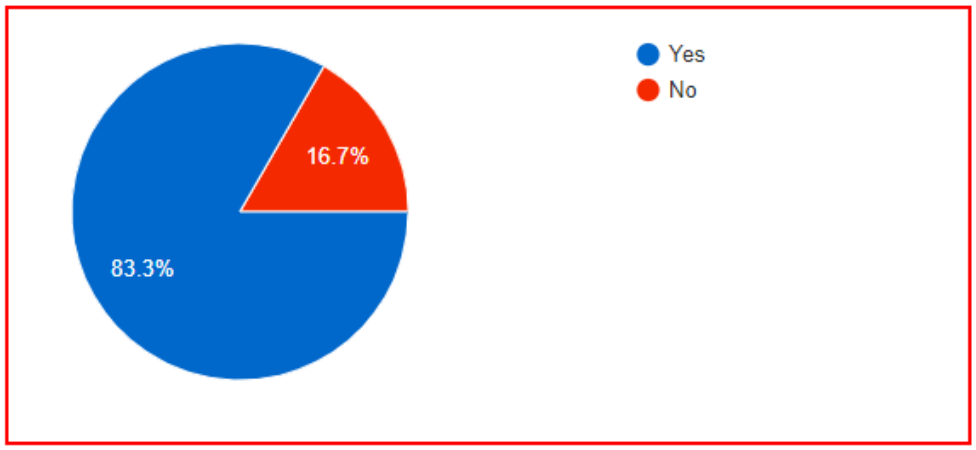


Figure 13: Acceptability of position and identification of schedules

There was reservation from one of the respondents who felt that whilst the prefixing of the schedule with the country name may help differentiate the schedules, there is still high possibility of confusion of the end users, mainly health professionals and patients. If confusion of patients is to be considered, then complete harmonisation of the schedules should be considered. Adoption of a recognized reference system, for instance the classification in the EU should be adopted.

The proposal to include a registration number panel was accepted by 83.3 % of the respondents. The reasons for not accepting this proposal by 1 of 6 (16.7 %) (*Figure 14*) of the respondents was that, while the respondent agreed in principle, there was a preference for using the wording 'marketing authorization number' instead of 'registration number'. On that note it was concluded that 100 % of the respondents agreed in principle to the mechanism being proposed;

Registration Number	Each country issues a registration number as the product is entered into a register. To enable harmonized labelling, it is proposed that a pane with all the registration details is set up on the label. The Country name and scheduling status will precede the registration number.	S3 South Africa NS3 Namibia RegNo.: POM Zambia RegNo.: S2 Botswana RegNo.: PP Zimbabwe RegNo.:

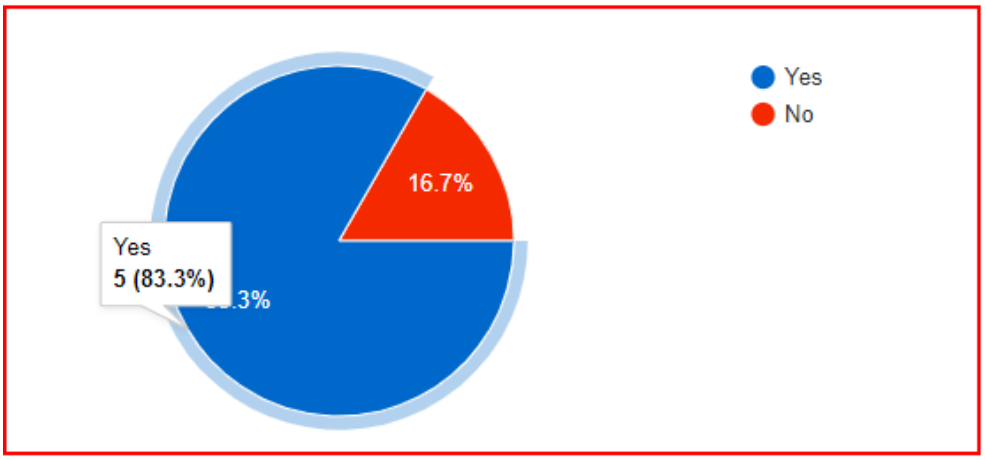


Figure 14: Acceptability of registration number panel

The harmonised framework will be further updated to address the preference by one of the countries on terminology for the registration number or marketing authorization number

For the rest of the requirements, 83.3% (*figure 15*) agreed to including any requirement that is not specified by their country in the labelling provided that it is value adding and is not conflicting with their country-specific requirements. These respondents indicated that legal provisions for incorporating requirements not specified in their own guidelines or regulations were available.

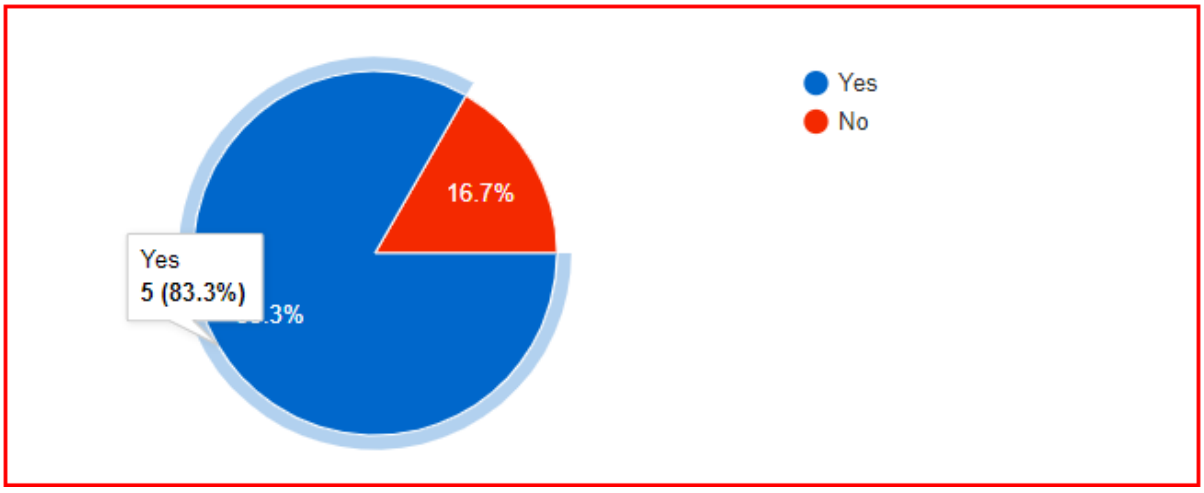


Figure 15: Countries with provisions for accepting additional information on labels

One respondent (Zimbabwe) indicated that such provisions did not exist as per their regulations. It is however proposed that legal opinion be sought on the applicability of Zimbabwean Regulations to Act 15:03 (S.I. 150 of 1991) section 37(1) (o) which provides for the authority to prescribe any other particulars to appear on labelling on this matter.

Despite the unavailability of legal instruments to allow incorporation of requirements from

some countries as per Figure 15 above, all countries (*Figure 16*) stated that the converged label could be implemented immediately.

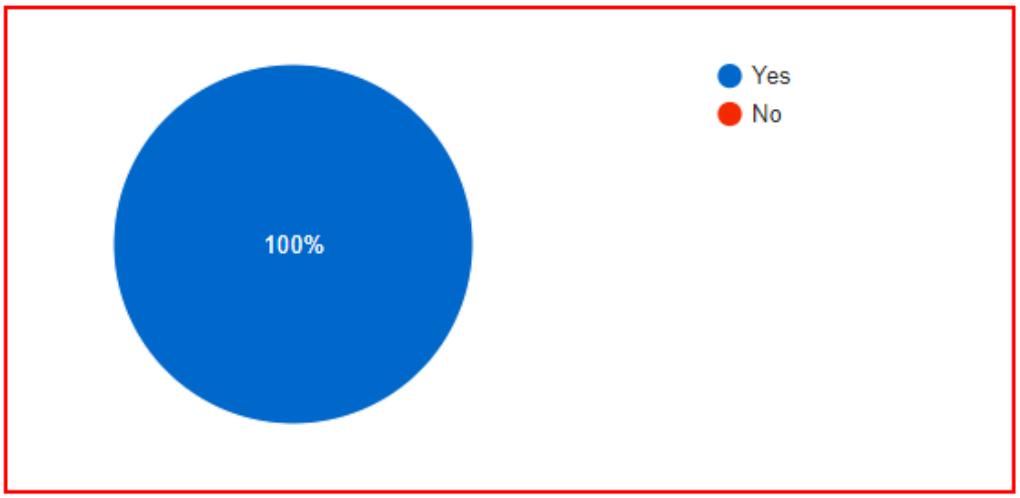


Figure 16: Applicability of interim provisions to expedite harmonisation

This a very important outcome as there is no impediment to the implementation of the harmonised label in the five countries represented in this study.

5.2. Acceptance of the Package insert harmonisation framework

All the respondents (100%) unanimously agreed that the EU structure of the package insert or SMPC might be used as a reference in deciding the format of package insert or SMPC to be adopted in the SADC region (see figure 17). This structure is a product of the harmonisation in the EU which culminated into directives, policies and guidelines actively being implemented by the EMA.

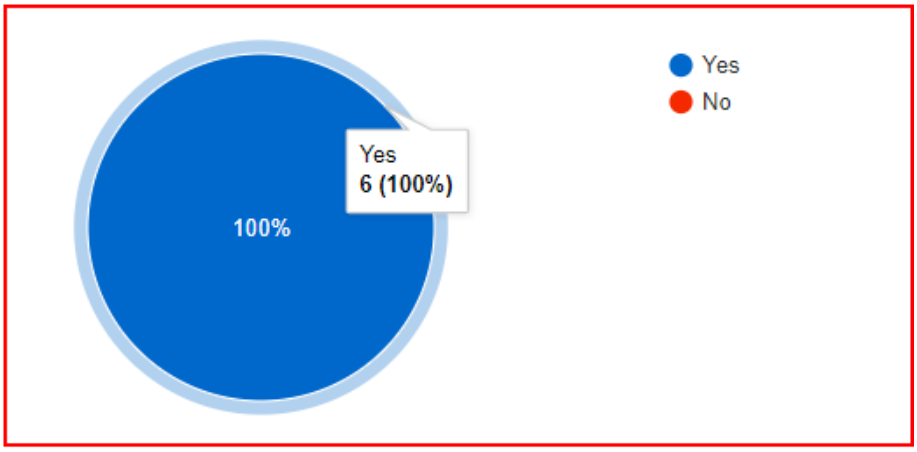


Figure 17: Acceptability of EU Package Insert / SMPC Structure as a reference for harmonisation

As with the labels, the majority of stakeholders (66.7%) (*Figure 18*) agreed in principle with the proposal to include all the unique country-specific details (Registration numbers, Pharmacological classifications, and scheduling statuses) for all countries on the harmonised Package insert as demonstrated in table 10. Of these stakeholders, 16.7% suggested that this should be accepted in the short term to expedite the harmonisation effort. In the long term, SADC stakeholders should consider adopting single scheduling classes and the same pharmacological classes. By doing this these unique classifications that exist will be eliminated. The idea of outright harmonisation was concurred with by one of the participants who did not agree to the proposal.

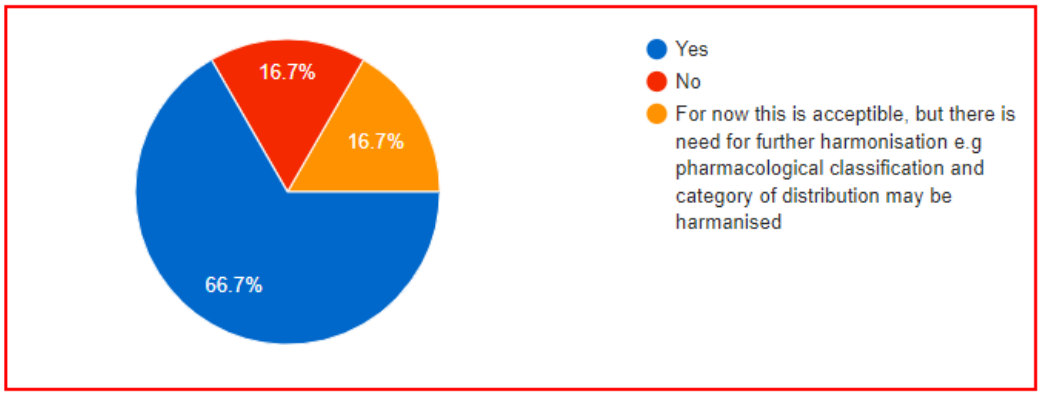


Figure 18: Acceptability of the format of presenting regulatory information on the Package insert

The content of Package inserts is derived from the pharmacological and clinical information obtained from the relevant studies. This informs sections such as indications, pharmacology, side effects, interactions, precautions. Also, a good part of this content comes from the established pharmaceutical details of the product such as composition, dosage form, strength, presentation, shelf life, etc. Over and above the pharmaceutical and clinical particulars, the rest of the information is based on the approved regulatory and prescribed legal requirements such as approved names, registration numbers, scheduling statuses, pharmacological classifications, etc. The recommendations for harmonisation of these sections has been discussed above.

Concerning the guidelines on labelling content which includes requirements for labelling of sugars in the products, standardised text for warnings and precautions, etc., the majority of the stakeholders, 66.7 % (*Figure 19*) did not accept this proposal. Of those objecting to this proposal, some expressed a sentiment that merely adopting what one member of SADC has done, infringes on the national sovereignty of the other members.

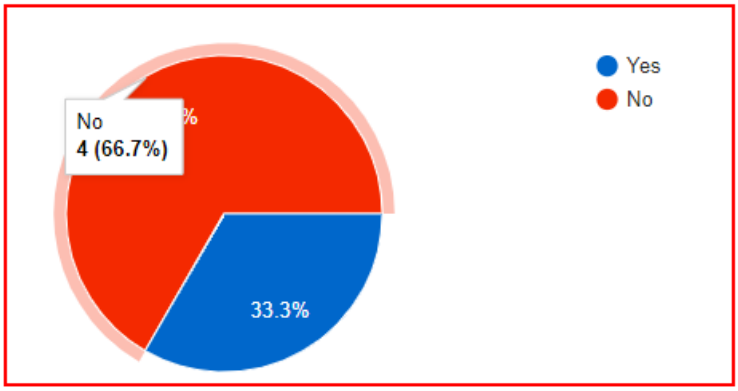


Figure 19: Acceptability of SAHPRA content guidelines as a reference for content harmonisation

One respondent stated a very important point that some of the practices in the member states are not in line with global practices. Adoption of guidelines from a recognised reference authority was then suggested e.g the EU. This could be a better solution to the problem as it averts the political issues that comes with converging to inherent practices by SADC member states.

The majority (83.3%) of the stakeholders objected to the proposal to use the South African approved innovator product package insert as the reference package insert. The use of the innovator product labelling approved by a stringent regulatory authority (SRA) was widely accepted instead.

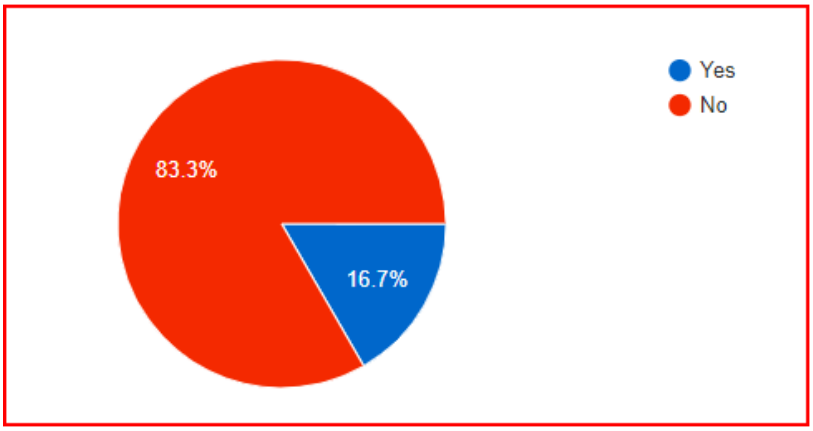


Figure 20: Acceptability of SAHPRA approved Package insert as reference

5.3. Changing the legal landscape to bring harmonisation

Despite the possibility of an expedited implementation of the harmonised framework using provisions to deviate from the prescribed legal code (*Figure 16*), update or change of the legal provisions is inevitable for the harmonisation project to be successful. All (100%) (*Figure 21*) the stakeholders in this survey declared their interest to initiate the requisite changes.

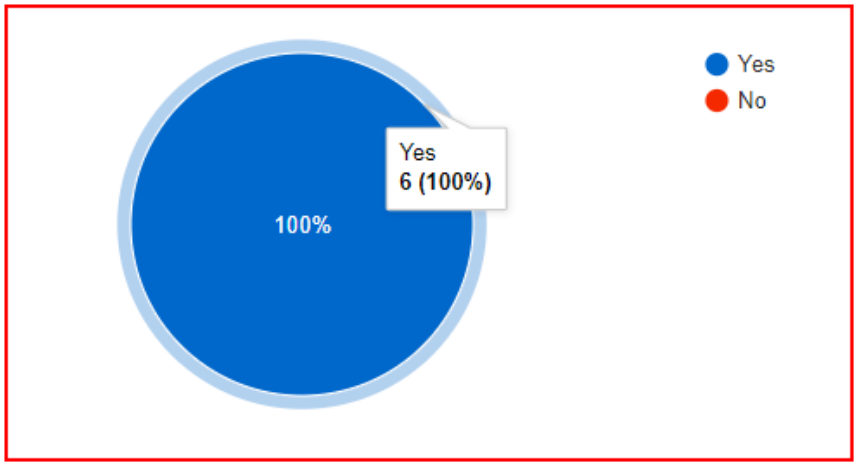


Figure 21: Declaration of will to initiate changes

Political will is a vital enabler for the harmonisation project, hence the declaration by stakeholders is a positive outcome.

As discussed before, the requirements for labelling are defined in acts, regulations and guidelines. 83.3 % (*Figure 22*) of the stakeholders confirmed that all the changes necessary to implement the harmonised labelling do not require a change to the principal act. This is also important because the legislative process required to amend an Act of parliament is an onerous process. The final amendment bill must be approved through voting by the highest legislative body in the country and only promulgated after the assent by the head of state. It follows that changes to the legal framework that do not require changes to the Act enables an expedited amendment process.

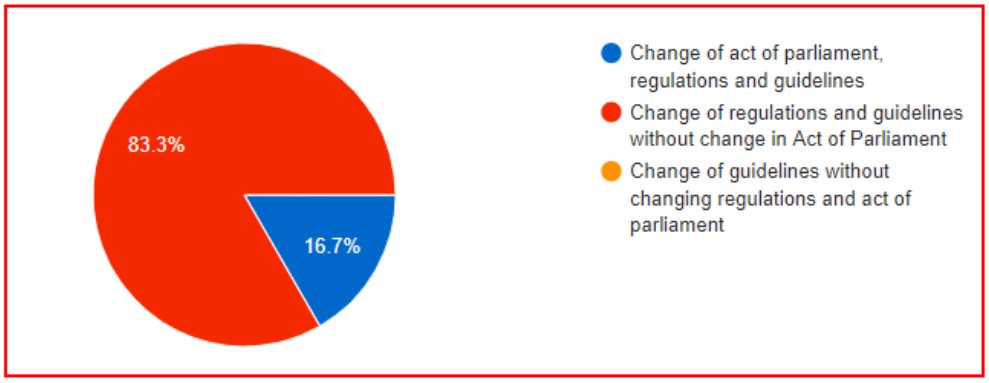


Figure 22: Regulatory & Legal changes required to facilitate harmonisation

The acts of parliament are considered primary legislation whereas regulations are considered subordinate or secondary or prerogative legislation. Changes to regulations in the countries surveyed are the prerogative of the minister of health in consultation with the relevant stakeholders. This simplifies the amendment process and hence harmonisation in SADC is achievable. Concerning the timelines for such changes, all the parties indicated that amendments could be achieved in 1- 4 years (*Figure 23*)

Figure 23 gives the perceived timeline for changes to the relevant laws to be made in support of regulatory harmonisation. The majority (66.6 %) of the respondents indicated that the relevant changes can be completed in 1 -2 years

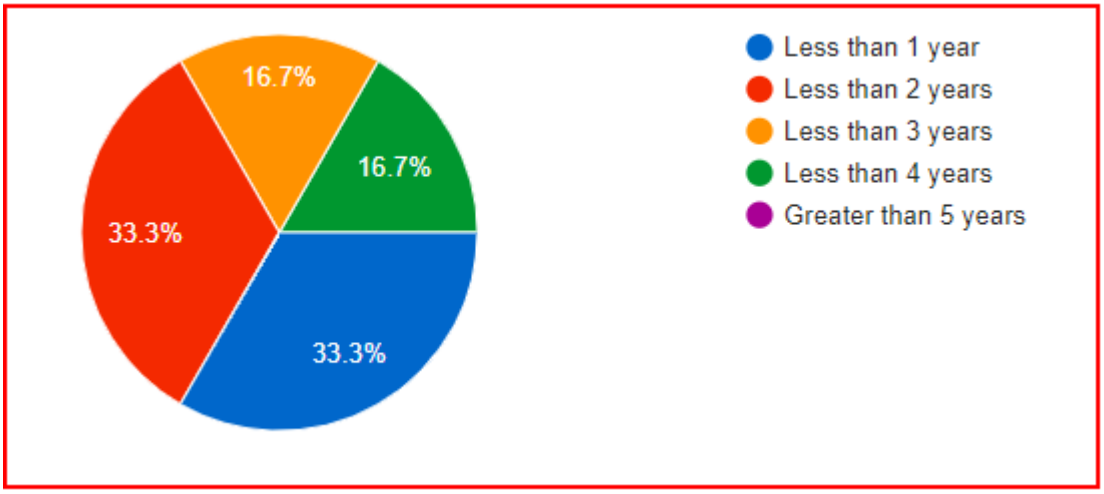


Figure 23: Timelines for changes in the acts or regulations

5.4. The potential impact of regulatory harmonisation in SADC

The harmonisation project's success is driven by the construct of the perceived benefits by the participating stakeholders. In the survey, a number of possible outcomes of the harmonisation project were reviewed to determine the perception of the parties involved. Participants were required to express their views using a linear scale illustrated in Figure 24.

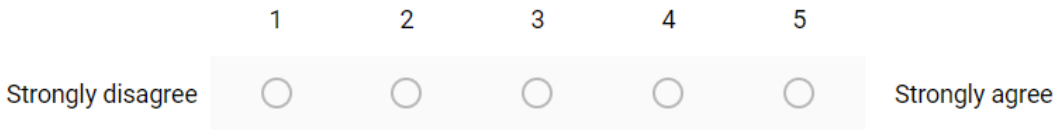


Figure 24: Scale for measuring perception

Harmonisation was perceived by the majority of the participants (80%) to positively impact public health in the SADC region *(Figure 25)* and the individual countries *(Figure 26).*

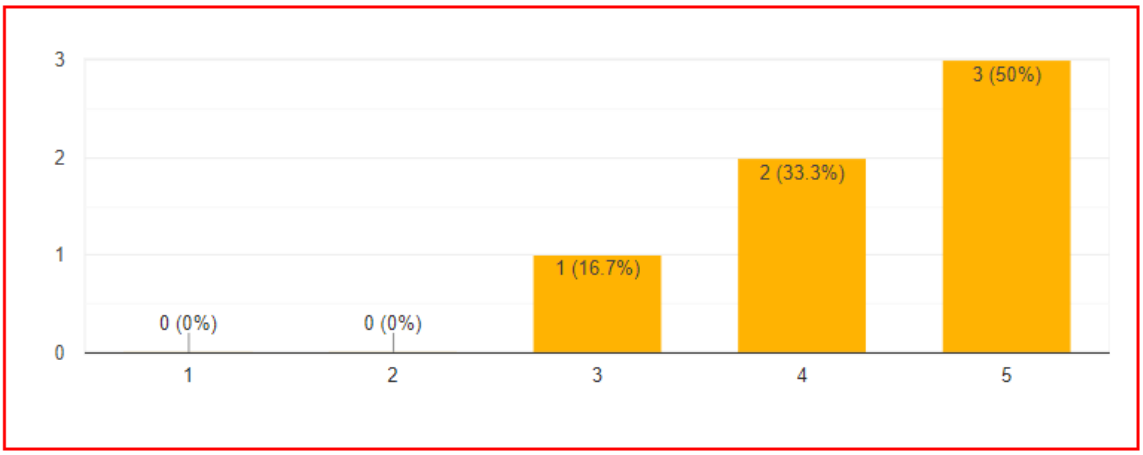


Figure 25: Potential impact of harmonisation on Public Health

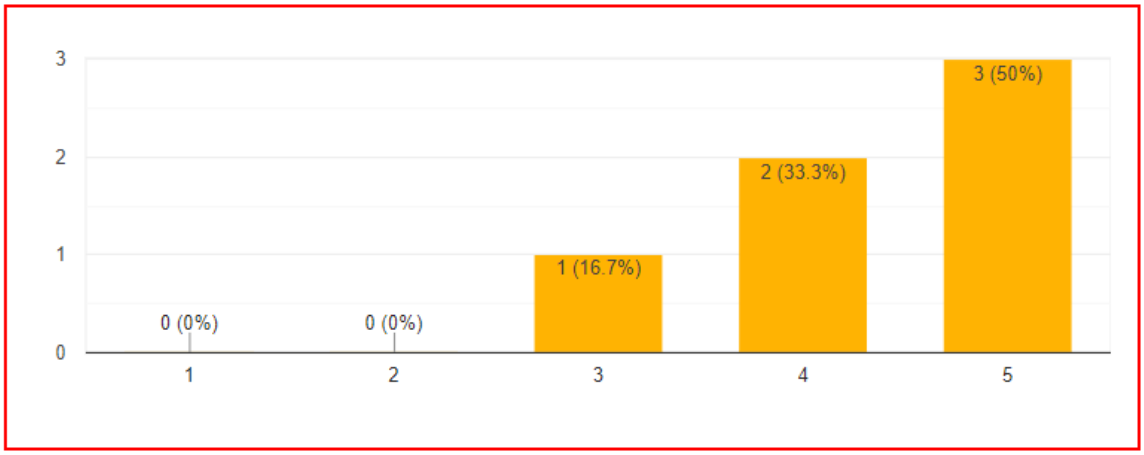


Figure 26: Potential impact of harmonisation on public health in the selected countries

The survey did not delve into specific ways harmonisation would impact on public health, however, 83.3 % (Figure 27) of the participants believed that labelling harmonisation will contribute immensely to the accessibility of essential medicines.

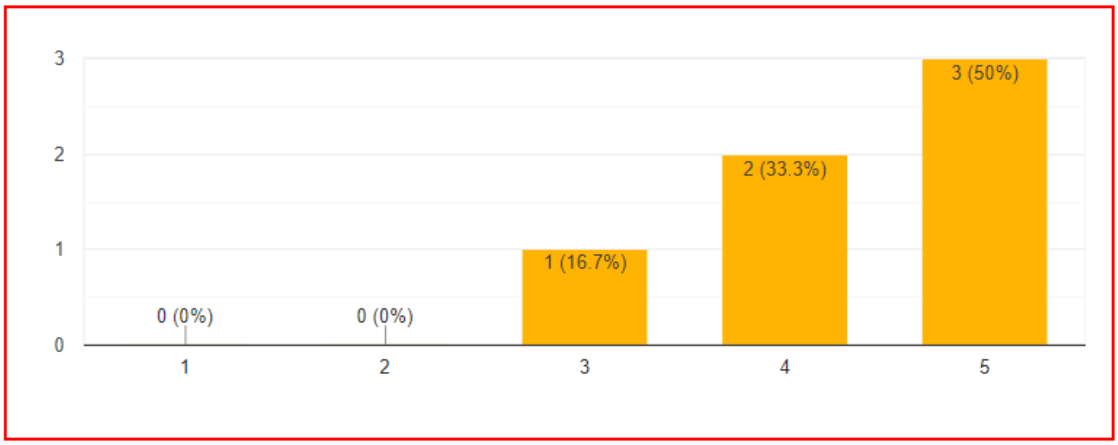


Figure 27: Potential impact of harmonisation on the accessibility of essential medicines

This is in line with the SADC Protocol for Health, in which pooled procurement is a key driver towards the goal of improved access to essential medicines in the region. Labelling harmonisation plays a significant role in enabling the pooled procurement of such goods.

Parallel importation is the legal mechanism applied in the importation and distribution of a genuine pharmaceutical products from a distributor in country (A), who legally acquired the same from the manufacturer at a lower price instead of buying directly from the manufacturer and then distribute in country (B). It was postulated that, harmonisation of labelling might facilitate this practice in SADC given the price differentials in the region. In this survey, the majority (60 %) of the participants perceived that parallel importation would not be a big issue for the SADC member states.

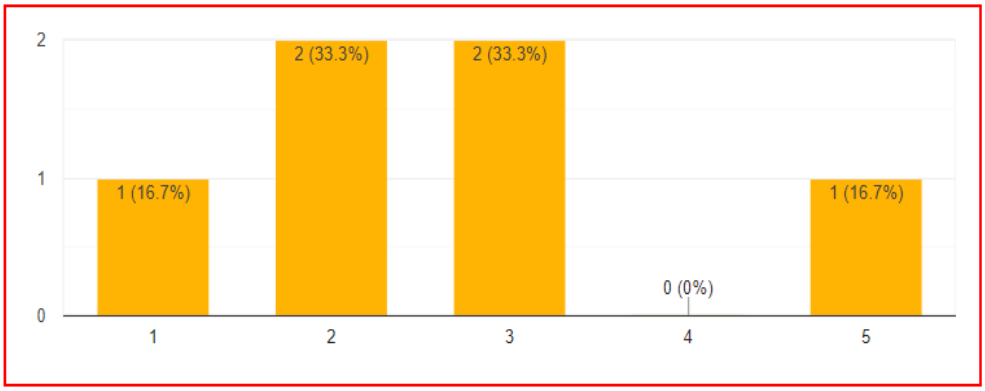


Figure 28: Potential impact of harmonisation on parallel importation

The participants also expressed (Figure 29) that the proposed regime on labelling does not have mechanisms to deal with parallel importation.

Figure 29: Ability of the harmonised framework to curb the illegal trade of medicines

Whilst it may be easier to do parallel importation when the labelling is the same or harmonised across countries, the control of illegal parallel import is a complex maze for many regulatory authorities. Though the participants did not think that illegal parallel trade would be a major problem in SADC, they (83.3 %) believed that if it happens, counterfeiting would be a major concern for the region. Illegal Parallel trade is believed to be a breeding ground for counterfeiting and comes with major health ramifications.

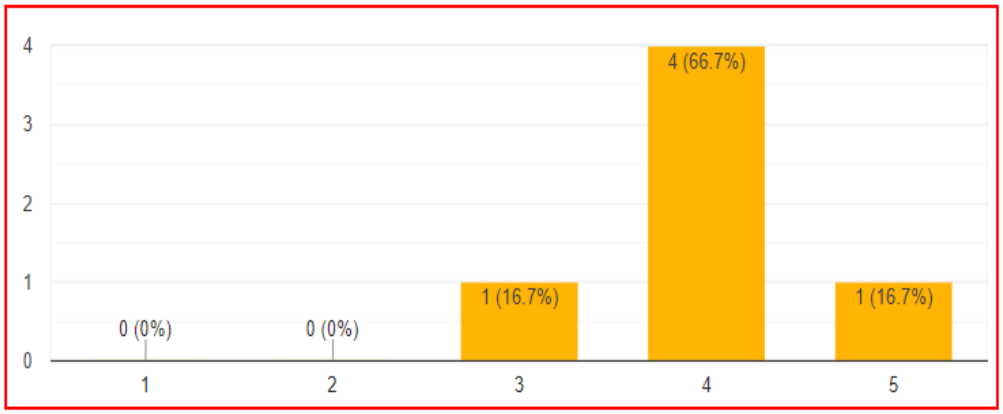


Figure 30: Potential impact of harmonisation on the counterfeiting of medicines in SADC

This, coupled with the perception (*Figure 31*) that the harmonised labelling does not provide sufficient measures to curb counterfeiting, may have dire consequences. It is recommended that the implementation of harmonised labelling should incorporate the implementation of anti-counterfeiting measures.

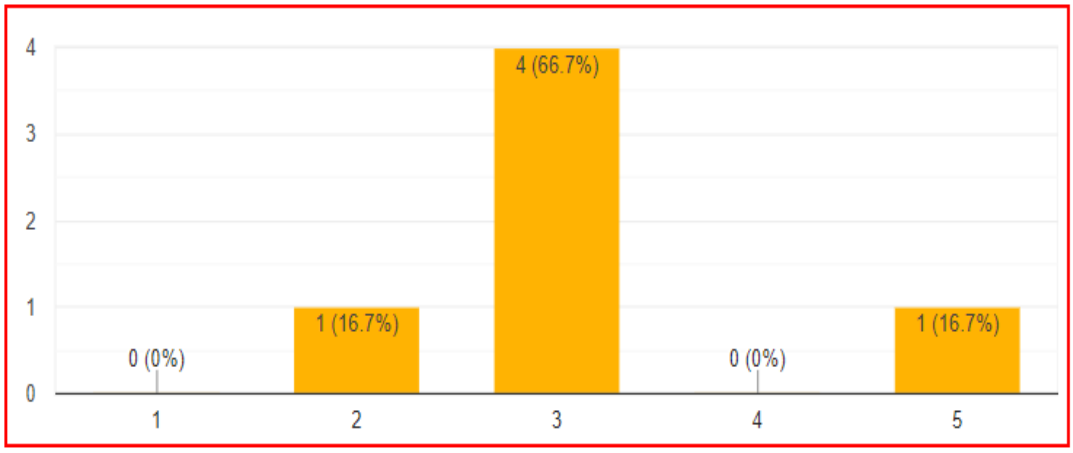


Figure 31: Adequacy of measures to curb counterfeiting in the harmonised framework

Overt and covert anti-counterfeiting measures including but not limited to special barcodes, holograms, UV based micro tagging and microchips have been proposed. This, however, is beyond the scope of this study.

The participants *(Figure 32)* also did not think that the harmonised framework would impact on the divergence of habit-forming drugs

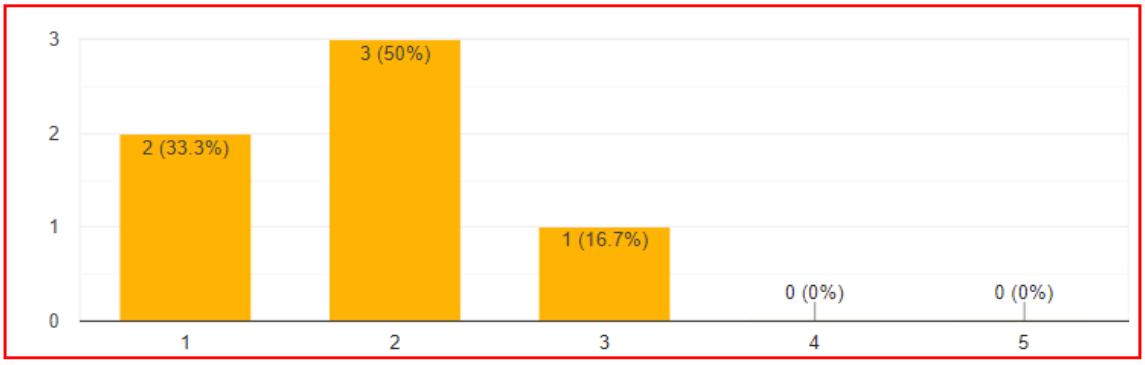


Figure 32: Impact on control of habit forming drugs

6. Discussion and Conclusion

The study aimed at developing a harmonised labelling conceptual framework that could be adopted in SADC. The concept development was informed by comparative analysis of the regulatory landscape in SADC as well as a head to head comparison of the prescribed requirements for labels and package inserts. This concept was validated by subjecting the proposed concept for assessment by different stakeholders including NMRAs, AMRHi and regulatory experts involved in harmonisation activities in SADC.

Comparative analysis of the legal requirements revealed that all the requirements for labelling are provided for in the regulations and guidelines. The principal legislation (Acts of Parliament) only stated that medicines should be labelled. This was confirmed by the stakeholders who indicated that for harmonisation to be achieved, amendments to regulations and guidelines only are required. The amendment of regulations is in the hands of the Minister of Health in consultation with the relevant stakeholders. It is therefore recommended that the conceptual framework developed in this study should inform the requisite changes to regulations for each country and such changes be spearheaded by the SADC Ministers of health through the NMRA Head of Agencies forum, coordinated by the SADC Secretariat. In this study, the support and political will to amend the regulations was apparent and the expected timeline as estimated by the stakeholders is 1- 4 years.

The outcome of the head to head comparison of the prescribed particulars categorised these into conflicting, unique and congruent requirements. This informed the harmonised labelling concept in which mechanisms to incorporate the unique requirements and resolving the conflicting requirements were put forward. This is fully described in in chapter 4 of this report in tables 8, 9 and 10.

The mechanisms proposed for the label was assessed by relevant stakeholders whose majority accepted the proposed changes with minor modifications. The proposed package insert harmonisation concept was also assessed by the stakeholders who agreed to the proposed format with a few changes. The EU SMPC structure was adopted as the validated format for SADC by the participating countries.

However, concerning additional guidelines for content, adoption of SAHPRA's additional guidelines was rejected on the basis that the current practices in most of the member states was not congruent with current global practices. It is recommended that guidelines from a

recognized reference authority, EU should be adopted/adapted for use by SADC member states.

Finally the major of contention was on the identity of the acceptable reference package insert. The innovator product registered in South Africa was not accepted. It is therefore recommended that package inserts in SADC be based on recognised approved package insert from a Stringent Regulatory Authority (SRA). It follows that the EU approved package insert is an accepted reference package insert for SADC.

On the basis of this agreed framework by Zazibona participating countries, the rest of the SADC member states may be engaged for wider adoption of the same. This will see the harmonised framework being adopted beyond the Zazibona region. The Zazibona adoption may become the nucleus for a wider corporation culminating into the SADC harmonised framework. On the backdrop of national sovereignty, it is recommended that the SADC secretariat engage the rest of the membership through a follow-up survey incorporating all the member states.

The public health benefits and the improved access to essential medicine should be the major driver in this project. Once achieved, the benefits will greatly simplify the supply chain for manufacturers and distributors. This holds true in the case where parallel importation becomes essential. Therefore the perceived benefits of harmonisation documented in this study should strengthen the resolve to expedite the harmonisation process.

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Appendix 1 – Ethics Approval

R14/49 Mr Givemore Mushayi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150863

NAME: (Principal Investigator)	Mr Givemore Mushayi
DEPARTMENT:	Pharmacy and Pharmacology Southern Africa Development Community
PROJECT TITLE:	Development and Validation of a Regionally Recognised Framework to Support Regulatory Harmonization of labelling Requirements in Southern Africa Development Community (SADC) Region
DATE CONSIDERED:	28/08/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Shabir Banoo

APPROVED BY: Professor P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 30/09/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date 10.10.2015

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 2 – Plagiarism Declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

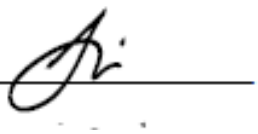
PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Givemore Muzuva Mushayi (Student number: 892170) am a student registered for the degree of Msc Medicine Pharmaceutical Affairs in the academic year 2018.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature:  Date: 24.10.2019