ASSESSMENT OF POTENTIAL BARRIERS TO MEDICINES REGULATORY HARMONIZATION IN THE SOUTHERN AFRICAN DEVELOPMENT COMMUNITY (SADC) REGION

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A Research Report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the Degree of Master of Science in Medicine (Pharmaceutical Affairs)

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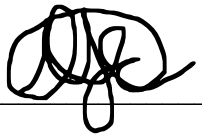
Declaration

I, Amanda Calder, 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 submitted before for any degree or examination at any other University.



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Abstract

Background

The World Health Organization (WHO) defines medicines regulation as the "promotion and protection of public health by ensuring the safety, efficacy and quality of drugs, and the appropriateness and accuracy of product information" (1). Medicines regulation is a key function in the realisation of the right to essential medicines. However, a satisfactory level of harmonization of regulatory activities has not been achieved in the Southern African Development Community (SADC) region as yet.

Objectives

The study evaluated the current status of medicines regulatory harmonization within the SADC region, as well as explored perceived barriers to regulatory harmonization and potential strategies to address these.

Methods

A cross-sectional exploratory study design with qualitative techniques, as well as an inductive approach was used. In-depth, semi-structured, face-to-face interviews with interviewees from the SADC Secretariat, the African Medicines Harmonization (AMRH) Initiative and the Southern Africa Regional Programme on Access to Medicines and Diagnostics (SARPAM) was used, involving secondary formal qualitative approaches to identify the emergent themes, was utilised initially. A questionnaire was formulated and adapted using secondary data collected from the face-to-face interviews, then piloted. Questionnaires were sent to senior members of all 15 regulatory authorities belonging to SADC, including registrars and deputy registrars.

Theoretical and analytical codes were identified from repeated ideas, concepts or elements. Codes were grouped into concepts, and then into categories. Trend analysis was conducted, involving an in-depth analysis of patterns.

Results

Barriers to regulatory harmonization in the SADC region perceived by participants included i) deficiencies in governance and leadership within the SADC Secretariat, ii) human resource and technical capacity constraints, iii) limited financial resources, iv) lack of political will within SADC governments, v) lack of intra-SADC relationships, vi) risk-benefit analysis differences in assessment of applications and bias according to local population needs, as well as vii) different guidance documents and legal frameworks among member countries. Strategies identified to address these included i) using other harmonization initiatives as models, ii) application format harmonization and African Union (AU) Model Law adoption, iii) redirecting focus of harmonization to information sharing and technical matter rather than complex legislative frameworks, iv) regulator initiatives of harmonization instead of SADC secretariat reliance, v) World Bank Agreement adoption, vi) human resource capacity development and vii) convergence of guidelines instead of complete harmonization of all regulatory requirements.

Conclusions

The findings in this study suggest that it may be necessary to redirect the focus of harmonization to more readily achievable activities and aim for convergence of guidelines. Regulatory harmonization is possible if barriers to it are addressed.

Key Words: *medicines regulatory harmonization, SADC, barriers*

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Abbreviations

AHC	APEC Harmonization Centre
AMRH	African Medicines Regulatory Harmonization
APEC	Asia-Pacific Economic Cooperation
API	Active Pharmaceutical Ingredient
ASEAN	Association of Southeast Asian Nations
ASEAN-NDI	ASEAN Network for Drugs, Diagnostics, Vaccines, and Traditional Medicines Innovation
AU	African Union
CTD	Common Technical Document
EAC	East African Community
ECCAS	Economic Community of Central African States
eCTD	Electronic Common Technical Document
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (of the United States)
GCC	Gulf Cooperation Council
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
ICDRA	International Conference of Drug Regulatory Authorities
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMP	International Drug Monitoring Programme
IGDRP	International Generic Drug Regulators Programme
IRS	Institute for Regulatory Sciences
IVDs	In-Vitro Diagnostic agents
MCC	Medicines Control Council
NCEs	New Chemical Entities
NEPAD	New Partnership for Africa's Development
NRA	National Regulatory Authority
PAHO	Pan American Health Organization
PANDRH	Pan American Network for Drug Regulatory Harmonization
PIC/s	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
RCOREs	Regional Centres of Regulatory Excellence
SADC	Southern African Development Community
SADCC	Southern African Development Coordination Conference
SAHPRA	South African Health Products Regulatory Authority
SARPAM	Southern Africa Regional Programme on Access to Medicines and Diagnostics
TB	Tuberculosis
UN	United Nations
WHA	World Health Assembly
WHO	World Health Organization
Zazibona	Pilot of collaborative registration procedures involving Zambia, Zimbabwe, Botswana and Namibia

Chapter 1 – Introduction and Review of the Literature

1.1 General Introduction

1.1.1 Background to the Research Study

The United Nations (UN) states that "the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition" (2). Although a complex matter, most countries have entrenched in their constitutions the responsibility to ensure that all citizens have available the highest level of "physical, mental and social wellbeing". This includes the "entitlements" of access to public health services and protection, the prevention and control of disease, as well as access to essential medicines.

Medicines regulation is a key function in the realisation of the right to essential medicines. The World Health Organization (WHO) defines medicines regulation as the "promotion and protection of public health by ensuring the safety, efficacy and quality of drugs, and the appropriateness and accuracy of product information" (1). Since the late 1990s, there has been a worldwide increase in innovation of pharmaceutical products, as well as increased access to new life-saving treatments through availability of generic products (3).

Capacitated health authorities are required to regulate emerging technologies and alternative health products, in the interest of public health. Drug development for priority public health diseases, such as the human immunodeficiency virus (HIV) and tuberculosis (TB) that affect developing countries is lower than that for diseases prevalent in developed countries. For example, in a study of 1393 new compounds brought to the market from 1975 to 1999, only 16 were developed for tropical diseases and TB. Drug research and development for these products should be promoted in the interest of public health and require efficient regulation to allow registration and availability in the market of developing countries (4).

Another example of a neglected disease was that of Ebola, which caused a rapid outbreak recently and resulted in the need to rapidly develop and regulate a vaccine (5). As a previously neglected disease, it gained publicity in 2013 through public outcry over lack of adequate treatment and control in Central African countries where it was spreading rapidly.

Likewise, the regulation of medical devices and in-vitro diagnostic agents (IVDs) are becoming a priority in many countries, which previously lacked the capacity to regulate and control these products. In order to regulate these products efficiently, there has been recognition by some countries of other countries' decisions to allow market access. For example, the Food and Drug Administration (FDA) of the United States recognises capacity constraints in its own system and allows market access to medical devices and IVDs which are registered in the European Union (EU) (6).

A study to assess the regulation of medical devices in the East African Community (EAC) was undertaken in 2012. It was found that the regulation of medical devices was generally weak, and that regulation pertained mostly to devices for priority diseases such as HIV, malaria and TB. Due to the lack of capacity to regulate medical devices of the regulatory authorities assessed, other research organisations and in-country laboratories were mandated to regulate these (7).

The use of traditional and complimentary medicines is often the most affordable and accessible healthcare option in many parts of Africa (8). The regulation of complimentary medicines has become a concern for many countries, due to the number of products entering the market of poor quality. There is the risk that these products may be substandard due to poor compliance with Good Manufacturing Practice (GMP) standards or that they may be adulterated with other substances (9). Complimentary medicines practices have also changed in modern times from the sale of a single substance to a mixture of different substances, which presents an even greater challenge in regulation (10).

Since 2011, complimentary products in the EU have been required to be licensed with a Marketing Authorization or a Traditional Herbal Registration (11). However, in many developing country settings, including sub-Saharan Africa, these products remain unregulated.

Cheaper labour costs in developing countries encourage an attractive manufacturing environment, while some regulatory authorities are concerned that this may be at the expense of quality. Many have argued that a lack of resources and corrupt practices are contributory factors to weak regulatory systems and oversight in these countries, leading to a knock-on effect on the quality of medicines available worldwide as well as an environment where counterfeit medicines are readily available. For example, it has been estimated that Nigeria's medicine market is comprised of 40% counterfeit medicines (12).

In a systematic review conducted in 2013 on forty-four prevalence studies on counterfeit medicines, mostly in low-income countries, it was found that the average prevalence was 28.5%, with most of these medicines containing insufficient amounts of active ingredient (13). The FDA estimates that over 10% of medicines on the global market are counterfeit, leading to inadequate therapy and poor public confidence in healthcare systems (14).

Medicines enable the healthcare system of a country to meet its public health mandate. However, medicines regulatory authorities in developing countries are struggling to keep up with the increasingly demanding regulatory environment for pharmaceuticals. This is largely as a result of limited regulatory capacity and the need to ensure access to safe, efficacious and quality products (15).

Substandard medicines may lead to drug-resistance and inadequate therapy. This also has the potential to impact adversely on the quality and safety of pharmaceutical products, leading to increase in availability of counterfeit

medicines. Furthermore, the availability of priority medicines to treat the specific burden of disease in countries may be compromised (16).

1.1.2. Regulatory Environment in Developing Countries

Many developing countries have poorly developed regulatory systems, procedures and processes to ensure adequate quality, safety and efficacy assessment or evaluation of medicines and other health products. This includes limited access to quality control laboratories, poor regulatory standards, lack of trained regulatory personnel and limited financial resources. In a situational analysis conducted by the WHO in 2010, it was found that 24% of countries in Africa had "basic regulatory capacity", 33% had moderate capacity and only 4% had capacity comparable to that of developed countries (17).

Furthermore, the capacity for the assessment of safety and efficacy of products, as well as on-going pharmacovigilance, is also lacking. This is hypothesised to be due to lack of technical capacity as well as resistance from stakeholders who benefit from low standards of regulation in the market (18). Improving medicines regulatory capacity requires human, financial and infrastructural resources, which are often lacking in developing countries (1). These themes were tested with stakeholders in this research study.

The limited capacity of countries in the developing world to regulate medicines has resulted in a number of cases of poor quality medicines being made available in these markets. It has been proposed that, due to lack of sufficient regulation, some pharmaceutical companies producing medicines for the developing and developed world may provide a sub-standard product to developing countries as compared to developed countries. This may include sub-standard packaging and inadequate amounts or quality of active ingredient (19).

Another challenge with the availability of medicines in many developing countries is the "Western Approval" barrier, where market approval from a

“stringent’ regulatory authority such as the FDA or European Medicines Agency (EMA) is often required before less-established regulatory authorities will approve an application (3). This has a major impact on time taken to approve registration of products and affects market access, especially for medicines used for diseases endemic to developing countries and not necessarily Western countries. This may become a barrier to harmonization for developing countries, as some require this approval while others do not take Western countries’ decisions as primary sources of confirmation of quality and safety of medicines.

Many developing countries are largely dependent on the importation of medicines from the developed world. When exported to developing countries, there is a concern that these medicines may not necessarily be scrutinized as much as when available locally (3). Developing countries need to work towards using regulatory decisions of other recognized authorities, while still maintaining autonomy and the ability to assess applications independently (20).

Although growing, pharmacovigilance activities in many developing countries, including sub-Saharan Africa, are severely lacking, with the first pharmacovigilance units with membership to the WHO’s International Drug Monitoring Programme (IDMP) being Morocco and South Africa in only 1992. Adverse Drug Reaction reporting remains low, which continues to highlight the weak regulatory systems of many countries in the region (21).

Currently, 33 pharmacovigilance centres in Africa are members of the WHO IDMP. Although many African countries have been the primary contributors of safety signals, such as those for the combination antimalarial agents, amodiaquine and artesunate, which cause extrapyramidal reactions, reporting on the whole remains low (22).

1.1.3. WHO Medicines Regulatory Harmonization Mandate

In 2008, the WHO estimated that only 20% of countries globally had efficient medicines regulatory bodies, with 30% of countries having very limited or no regulatory systems for health products. More than two-thirds of the world lives in areas with high disease burdens and where medicines are not regulated effectively (18).

In 1975, the World Health Assembly (WHA) called on the WHO to be of greater assistance to member states regarding medicines regulatory systems. The WHO conducted studies in 1999, 2002, 2003, 2007 and 2010 pertaining to this. The 2010 country profile pilot study for 12 countries, with varying disease burdens and regulatory capacity, was analysed and resulted in the conclusion that regulatory systems differ in funding systems, legal provision for clinical trials and pharmacovigilance, as well as Good Distribution Practice (23).

The WHO has an international mandate to support member countries in improving public health globally (24). This has also involved providing support for improving medicine regulation in developing countries through training and capacity building as well as the development of regulatory procedures and guidelines. This has also involved support through the WHO Certification Scheme and quality control laboratories, as well as the WHO Medicines Prequalification Programme (1).

The WHO Certification Scheme is an international agreement that provides assurance of the quality of a finished pharmaceutical product. It allows member states to issues Certificates of Pharmaceutical Product to confirm that a product has received market authorisation in a country and has been manufactured according to GMP (25). This is useful for developing countries that wish to export their products to other countries to prove compliance with WHO regulations.

The WHO Medicines Prequalification Programme has been effective in increasing capacity of regulatory authorities for GMP inspections through training of inspectors. It also provides a list of products that meet current GMP standards, while still encouraging autonomy of regulatory authorities with regards to assessment for market authorisation and post-marketing surveillance. However, the prequalification programme has been criticized as allowing lower standards than those of more stringent regulatory authorities as well as that required by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (26).

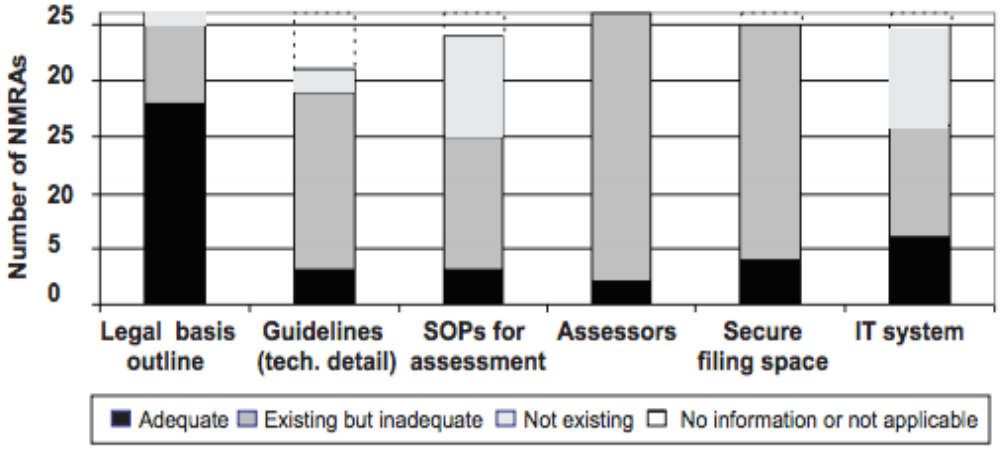
The Prequalification Programme is more focused on generic medicines, while the ICH guidelines are focused on New Chemical Entities (NCEs). WHO prequalification standards are applied to essential medicines, and therefore play a priority role in Africa, where the majority of medicines used are primarily generic products. It has been found that the ICH harmonization process is a costly and time-consuming exercise, which has involved stakeholder commitment and funding to reach its current status. ICH guidelines are applicable to NCEs, rather than generic products that are more common in the developing world (26).

The fact that the developing world may find the WHO standards more viable and that the perceived gap in quality of the WHO and ICH standards may affect willingness of regulatory authorities to harmonize, especially with regards to generic medicines requirements. The ability and willingness of regulatory authorities in SADC to comply with harmonization standards was also the subject of this study.

The WHO has also chaired the International Conference of Drug Regulatory Authorities (ICDRA) since 1980, which provides an ideal platform for networking and communication between WHO member states on regulatory activities and advances (24).

A study was conducted by the WHO between 2002 and 2009 to assess the state of medicine regulation in 26 countries in sub-Saharan Africa. This study found that regulatory authorities in most countries were financially and human resource constrained. It also found that there was a lack of autonomy and almost no ability of the regulatory authorities in developing countries to evaluate innovator applications, as these require a more complex review process than with generic applications. A total of 92% of the countries noted that a lack of qualified experts to evaluate the regulatory dossiers inhibited the efficiency of the regulatory authority. These findings were summarised in the FIGURE I below, from the WHO report (27).

FIGURE I: Resources for Medicines Registration (27)



Conclusions drawn from the study to address the constraints listed involved increasing political will and to increase capacity of regulatory authorities through harmonization, training and other support from the WHO and other regulatory authorities (27).

1.1.4. Harmonization in the European Union (EU) and the International Conference on Harmonization (ICH)

Events such as the Tuskegee tragedy, involving the injection of African-American patients with syphilis for the purpose of conducting clinical trials, led to the implementation of clinical research policies and legislation worldwide, including the Nuremberg Code in 1947 and the Declaration of Helsinki in 1964 (28). There also emerged the realisation of the need for medicines regulation to avoid events such as the Thalidomide tragedy in the 1950s and 1960s, involving severe malformations in thousands of babies born to mothers who had consumed the medicine to treat nausea (29).

A framework of minimizing duplication of medicines regulatory activities and clinical trials was needed, as well as to reduce the need for animal testing (28). This led to a valuable initiative to promote effective harmonization of medicines regulation with the creation of the ICH in 1990. This tripartite alliance of Europe, Japan and the United States was successful in avoiding duplication of registration requirements (3).

The Common Technical Document (CTD) format was developed to improve efficiency by reducing costs and maximizing human resources by reducing time to reformat registration dossiers for medicines. The CTD is a common, harmonization application format that consists of five modules – Module 1 is specific to local requirements of regulatory authorities, while Module 2 to 5 are common to all applications (30). The CTD format was finalised in November 2000 and has since been adopted by the ICH countries as well as many countries outside of the ICH (31). The CTD format also helps to bring products to the market in multiple countries more efficiently, using a "common regulatory language". This is significantly important in low-income countries, with a lack of expert resources (3).

In addition to the ICH framework for regulatory harmonization, there is mutual recognition that exists between the country regulatory bodies within the EU, including a centralised registration procedure, which enables diversification of skills of the participating regulatory authorities as well as opportunities for learning outside of a country's borders (24). The centralised procedure came into effect in 1995, where applications are sent directly to the EMA for review. The applications are then assessed by the Committee for Medicinal Products for Human Use or Committee for Medicinal Products for Veterinary Use, as applicable. Once the committee approves the registration of a product, the registration is valid in all EU member states for five years (32).

Other methods of registration are possible in the EU, such as mutual recognition, where a product may be registered in one country and then on subsequent application to other countries in the EU, under this procedure, regulatory authorities do not undertake full evaluation of the application, but use the regulatory decision made by the first country. For products outside of the EMA's scope, applications may be sought from each regulatory authority simultaneously (33). This is a system to which other Regional Economic Communities, including SADC, may benefit from.

As a further means for supporting regulatory decisions in developing countries, the EMA works with the WHO to form a scientific opinion of products that "are intended exclusively for markets outside of the European Union". These medicines used for public health benefit to treat diseases not highly endemic to the EU including treatment for HIV, malaria and TB, as well as vaccines for WHO priority diseases. The products on which an opinion is formed are not registered for use in the EU, but an opinion is sent to the WHO and non-EU regulators to enable regulatory decision (34).

However, the wider adoption of the CTD/eCTD format within the EU region remains limited and many countries continue to use older application formats (35).

The EMA and FDA have a cooperative agreement, which includes information sharing of pharmacovigilance data, paediatric studies and audit reports (36).

Currently, the majority of the regulatory authorities in the world, mostly in emerging economies, do not belong to ICH, although many now have observer status. These countries find that the WHO standards are more viable to implement than ICH, which many have suggested are more costly and require greater human resource and technical capacity to implement. The WHO prequalification standards have been viewed by some as less stringent than the ICH standards (26). For example, ICH guidelines for stability testing require three batches of product to be tested, while the WHO guidelines require only two (37).

In a study conducted by Specht and Klingmann in 2014, 30 subjects from the European pharmaceutical industry and regulatory authorities were interviewed to discuss successes and failures of the ICH. In the study, concerns were expressed that regulatory authorities in developing countries may not have the financial and human resources needed to contribute to the work of the ICH and conform to its standards (38). Several participants in the study conducted by Specht and Klingmann expressed concerns that ICH guidelines need improvement and that implementation should be enforced in a stricter and more efficient way. The need for better cooperation among regulatory authorities was also highlighted by the study (38).

1.1.5. Regional Regulatory Harmonization Efforts

1.1.5.1. Association of Southeast Asian Nations (ASEAN) Region

The Association of Southeast Asian Nations (ASEAN) Region consists of 10 member countries (Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand and Vietnam) (24). This was the first region to introduce limited harmonization of regulatory functions and activities in 1967 to increase pharmaceutical trade, with a focus on mutual recognition of GMP standards and inspections (20). The region consists mainly of middle to lower

income countries, with many challenges to healthcare in the region including a neglected tropical disease burden, TB, avian influenza, as well as non-communicable diseases (39).

To address the burden of diseases specific to the region, these countries developed the ASEAN Network for Drugs, Diagnostics, Vaccines, and Traditional Medicines Innovation (ASEAN-NDI) in 2009, aimed at promoting research and development of pharmaceuticals to treat priority diseases in the area (40). The ASEAN Sectoral Mutual Recognition Arrangement for GMP for Manufacturers of Medicinal Plants, recognising GMP certificates and inspection reports, was signed in 2009 in an effort to avoid duplication of efforts. The ASEAN Common Technical Dossiers and ASEAN Common Technical Requirements have been developed to ensure harmonized quality, safety and efficacy requirements for applications for registration in the region (41).

1.1.5.2. Asia-Pacific Economic Cooperation (APEC)

The Asia-Pacific Economic Cooperation (APEC) was created in 1989 consisting of 21 countries, including Australia, China, Hong Kong, Canada, Japan, USA and many regulatory authorities that also belong to other regulatory harmonization initiatives in the Pacific Rim (24). The APEC Harmonization Centre (AHC) was developed in 2009, aimed at harmonization of regulatory requirements for medicines and medical devices in the region (42).

Although medicines harmonization activities in the region were only recently established, much progress has been made to date in developing harmonization review processes. The region has developed a "2020 Good Review Practices Roadmap" to coordinate harmonization of medicines regulatory requirements in the region. A number of workshops have been held to agree on the basics of the review process and to promote best practices, including one in 2014 with 133 representatives from 20 countries in the region (43).

1.1.5.3. Gulf Cooperation Council (GCC)

The Gulf Cooperation Council (GCC) was created in 1981 and consists of 6 Arab states (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and United Arab Emirates). The Gulf Central Committee for Drug Registration coordinates policies and information sharing, including with GMP inspections (24).

The GCC established a centralised review procedure for NCEs and generic medicines using a GCC Central Drug Registration Committee in 1999. The process for review involves two authorities assessing the application for registration with the other countries being provided with copies of the application (44).

However, there have been concerns from the pharmaceutical industry that harmonization initiatives in the region are increasing medicine registration times. A study conducted by M.H Al-Rubaie *et al* in 2013, involving 413 products that were reviewed by the GCC centralised review process, found that the mean time taken to review applications had increased from 2006 to 2010, and was attributed to time-consuming centralised review processes (45).

1.1.5.4. Pan American Health Organization (PAHO)

The Pan American Health Organization (PAHO), together with the WHO, created the Pan American Network for Drug Regulatory Harmonization (PANDRH) in 1999. This has focused on training and the establishment of common technical guidelines on GMP, pharmacovigilance and other regulatory activities within the region (24).

The PANDRH began working with regulatory authorities in the region in 2000 to build capacity, including in the areas of licensing of manufacturers, product quality, safety and reducing counterfeit medicines. This has involved establishing a network of laboratories and pharmacovigilance activities, as well as registration

activities. The regulatory authorities of Argentina, Brazil, Canada, Colombia, Cuba, Mexico and the United States were designated as models for regulatory excellence for other countries in the region (46).

The PANDRH holds regular conferences to discuss regulatory harmonization in the Pan American region and systems to overcome challenges in the area. In September 2013, the seventh PANDRH meeting was held in Ottawa, Canada, with a focus on pharmacovigilance, medicines regulatory harmonization promotion and the development of mechanisms for regulatory training. This meeting acknowledged the need for improvement in the area of regulatory sciences and countries were given the mandate to develop regulatory capacity through "competency-based" curricula at training institutions (47).

1.1.5.5. African Medicines Regulatory Harmonization (AMRH) Initiative

The International Conference of the Drug Regulatory Authorities (ICDRA) is a forum for regulatory authorities to discuss challenges in medicines regulatory affairs worldwide, as well as to discuss solutions. It is a meeting of global regulatory authorities to exchange ideas and collaborate on initiatives, including regulatory convergence and harmonization (48).

At the 13th ICDRA meeting in 2008, consisting of more than one hundred United Nations (UN) member countries, concerns were raised about the need for harmonization in many regions of the world and particularly in Africa. This resulted in the AMRH Initiative being established (49). The initiative divided African countries into 5 regional groups, with a 5-year project plan. Of these, the Economic Community of Central African States (ECCAS), SADC and EAC are the most advanced to date (36).

An African Regulatory Conference was held in Johannesburg in 2010 to further these objectives and was attended by regulators from forty countries in Africa. Here, the WHO reiterated that shared knowledge of product assessment would

improve harmonization by minimising repetition of work efforts and thus improve quality of public healthcare (36). The WHO, amongst others, provides support to developing countries in establishing common technical and administrative requirements such as the use of the CTD format for submission of registration applications and ICH standards, as well as encouraging collaboration with the inspections of manufacturing facilities. The activities of the AMRH Initiative to assist with regional harmonization on the continent are also supported by the Bill & Melinda Gates Foundation and the World Bank (49).

The AMRH Initiative is a technical unit of the African Union (AU), responsible for facilitating and implementing regional initiatives and encouraging communication between stakeholders. The AMRH Initiative's main strategic areas of focus include policy and regulatory framework harmonization, capacity development, improving communication and an enabling environment for regulatory harmonization through monitoring systems, as well as sufficient control and networks for sharing of knowledge (50). The AMRH Initiative aims to enable countries to move towards achieving their Millennium Development Goals (51).

It has been noted by the AMRH Initiative that accountability by member states is important to ensure optimal coordination of harmonization activities. Priority areas such as regulation of medicines should be attended to before focusing on other regulatory functions. Registration may be used as a pilot to establish how other functions may be addressed (50). Sovereignty of the countries is imperative in this process. Critical milestones for regulatory harmonization were proposed by the AMRH Initiative (52), which were adapted in TABLE I below.

TABLE I: Critical Milestones for Regulatory Harmonization

Level of Harmonization →

Independent	**Regulatory Convergence**	**Harmonized Standards**	**Centralized Regulation**
Each authority has its own standards	Information Sharing	Joint evaluations and inspections	Registration on behalf of participating authorities
Own specific requirements for registration	Harmonization GMP Guidelines	Mutual recognition of decisions	
	Harmonized registration requirements	Quality Management Systems	
		Management Information Systems	

Adapted from African Medicines Harmonization Initiative (52)

1.1.5.6. East African Community (EAC)

The first successful regional group of the AMRH Initiative has been that of the EAC Medicines Registration Harmonization project, which was started in March 2012 and involves Uganda, Kenya, Tanzania, Rwanda and Burundi (49). The project involves a combined effort in the assessment and approval of medicine registration applications, as well as common standards for manufacturing facilities (according to GMP and Quality Management Systems) and technical requirements. The EAC has since become a member of the ICH Global Cooperation Group, attending meetings and being exposed to knowledge sharing with other regulatory harmonization initiatives such as the APEC Regulatory Harmonization Initiative (36).

Support from the World Bank with regards to funding and expertise has been a major contributor to the EAC's successes in harmonization. The World Bank has

recently agreed to provide similar funding to SADC. However, the difference with the EAC and SADC is also suggested as being due to the similarities in regulatory capacity of the EAC countries. Within SADC, country capacity varies greatly from Zimbabwe and South Africa who are seen as having relatively well-developed regulatory bodies to Swaziland with a very poorly developed regulatory authority, consisting of only two evaluators.

The EAC has a mandate to facilitate regional cooperation including in health, through enabling regulatory harmonization. A great deal of consultation between regulators, industry and policy-makers has enabled the establishment of a governance structure, with a project steering committee and technical working groups (50). The EAC has made significant progress towards harmonization of regulatory requirements, including producing regulatory tools and guidelines, organizing joint inspections along with the WHO as well as building harmonized information systems (53).

Endorsement from stakeholders is a key area of implementation that has been identified by the EAC. The success of regional initiatives will establish a foundation for a single African medicines regulatory body. Cooperation, commitment and collaboration by all stakeholders are key (50).

1.1.5.7. Southern African Development Community (SADC)

Many consider the origins of SADC, originally the Southern African Development Coordination Conference (SADCC), to have been from the "political alliance" of countries in Southern Africa in fighting against white oppression in the 1970s (54). SADCC was established in 1980 to improve economic development in the region, with each country being responsible for a different sector within the region. The organization has historically provided poor communication and a lack of cohesion between member states, and economic instability has led to an over-reliance on donor funding in most of the region (55). The SADC region currently consists of fifteen countries, including

Angola, Botswana, Democratic Republic of Congo, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Swaziland, Tanzania, Zambia and Zimbabwe (56).

The SADC Health Protocol for Regional Cooperation and Integration has been in existence since 1999 and forms the basis of regional health governance and collaboration (24). The SADC Protocol on Health provides a framework for cooperation and integration of health policies to alleviate the burden of diseases prevalent in the area, such as HIV, TB and malaria. The protocol provides strategies, including regulatory integration, to achieve the goal of "Health for All" in the member countries by 2020 (49). SADC developed a Health Policy Framework, which was approved in 2000. This focused on "health research and surveillance, health information systems, health promotion and education, HIV and AIDS and sexually transmitted diseases, communicable and non-communicable disease control, disabilities, reproductive health, health human resources development, nutrition and food safety, and violence and substance abuse" (57).

However, a satisfactory level of harmonization of regulatory activities has not yet been achieved in the SADC region. Potential barriers to harmonization may relate to differences in the organizational structure of regulatory authorities within the region, differing legislative and regulatory provisions as well as different levels of technical capacity for regulation among member countries (24).

Whilst the literature appears to be sparse with regards to assessments of regulatory harmonization in Africa and the SADC region in particular, a study conducted by Narsai *et al* in 2012, involving 33 members of pharmaceutical companies in South Africa with a presence in other SADC countries, investigated obstacles to regulatory harmonization within the SADC region. This study revealed that barriers to availability and accessibility of quality, safe and efficacious medicines to the markets within the SADC region were mainly due to resource limitations. Pharmaceutical companies interviewed stated that they were reluctant to export

their products to certain countries within the region due to different requirements and costs such as for registration, retention and inspection. 82% of pharmaceutical company representatives that participated in the study were in favour of harmonization of legislative frameworks for medicine regulation (58).

The study recommended that the SADC region harmonize legislation requirements as soon as possible, which will benefit pharmaceutical industry, patient groups and healthcare professionals. It also recommended evaluating regulatory requirements to assess essential requirements, in an effort to reduce the time taken for the registration of products (58).

1.1.5.8. Zazibona

Frustrated with the time delay in SADC harmonization attempts, the regulatory authorities from Zambia, Zimbabwe, Botswana and Namibia embarked on an initiative to pilot harmonization in the region. This collaboration was termed "Zazibona" and has resulted in the successful registration of a number of products, as well as reduced the average of 24 months' registration time to 9 months. The initiative focuses on registration of products for ten priority diseases in the region, including TB, HIV and malaria (59). The four countries have also undertaken joint inspections, where manufacturing facilities have been inspected for GMP compliance (60). Other member states in the region such as South Africa have also been invited to participate in this pilot initiative.

1.1.6. World Bank Agreement

The World Bank has provided funding for the EAC harmonization initiative since 2011 (61) and initially rejected the proposal sent by SADC, but has recently agreed to fund the SADC regulatory harmonization initiative with a 5-year duration.

The goals of the initiative are to "improve the availability of medicines through the regional harmonization of regulatory systems, guidelines and processes among Member States in the SADC through:

• Harmonizing the system of medicines registration and broadening the scope of products reviewed (NCEs, vaccines and biologicals) and regulatory functions undertaken (clinical trial oversight, pharmacovigilance etc.),

• Achieving political, legislative and financial support by communicating the value of the project to all stakeholders,

• Building regulatory capacity and capability, and

• Sharing information to facilitate faster decision making" (62).

Another key goal of the initiative is to "develop and implement national and regional management information systems". This will address the barrier of lack of information sharing and transparency by creating such a platform. Creation of a Quality Management System and Monitoring and Evaluation System are key goals that, if implemented, will enable implementation and monitoring of adherence to guidelines and procedures, ensuring optimal performance (62).

1.1.7. The Need for Global Regulation

The increasing globalisation and decentralisation of the pharmaceutical industry affects regulatory issues worldwide. The United States of America currently imports 80% of its active pharmaceutical ingredients for pharmaceuticals and the FDA regulates products manufactured at about 300 000 manufacturing sites in the world. Many of these sites are located in countries with regulatory systems viewed as "weak" by the FDA, including India and China (12).

A weak regulatory system in one country may have a substantial impact on many others, if the country produces active ingredients, other excipients or products for other countries. Although the FDA is seen as a "stringent" regulatory authority, it has recognised that the quality of the pharmaceutical products in the United States

is impacted by less developed regulatory authorities (63). The FDA has therefore identified a need for harmonization on a global scale (12).

Although regional harmonization efforts have proved relatively successful in some cases, a global regulatory framework to encourage a sustainable approach to addressing these issues may be needed. This would result in a more coordinated framework for capacity building, improved transparency and overall quality of pharmaceuticals. Global regulation in other industries has shown that without accountability, individuals and organization lack the sense of urgency and commitment to adhere to rules and regulations (12).

The Council on Foreign Relations, an independent advocacy organisation in the United States, indicated in September 2013 that "success of global regulatory schemes developed in other sectors appears to be contingent on five distinct stages: agenda setting, negotiation, implementation, monitoring, and enforcement". A multi-sectoral approach, including all stakeholders in medicines regulation such as the non-profit, academic, private and government sectors, is necessary to ensure sustainability and cooperation. The strengths and resources that each sector brings in medicines regulatory affairs will enable an increase of capacity and communication. This in turn will lead to greater trust in the regulatory system (12).

With the rising costs of medicines development, a collaborative public-private approach on a global level for medicines regulation is imperative. An example of a functional global harmonization standard is the use of bankcards to enable currency withdrawal from most ATM machines throughout the world. In order to ensure successful implementation, standards should be able to be enforced by regulators. A key method to enable this is the inclusion of provisions in health product legislation that allows the regulator to adequately enforce penalties if standards are not upheld.

Harmonization of medicines regulatory activities encourages sharing of information and technology, and promotes better access to medicines (1). The available literature supports the view that harmonization would be beneficial to all parties in a healthcare system. It consists of synchronization of scientific requirements for regulatory applications, leading to acknowledgement of scientific data, as well as synchronization of format and procedures for review that aids evaluation and approval (35).

The literature also suggests that on harmonization supports capacity building of medicines regulatory authorities through utilization of expertise from other countries, as well as improved public perception. Pharmaceutical companies would also increase profitability by globalization. Patients would gain better access to effective pharmaceuticals, also reducing costs incurred to them and the healthcare system of the country (58). However, barriers exist to achieving this goal, which were explored in this study.

1.2. Problem Statement

The current lack of regulatory harmonization in the SADC region significantly undermines the availability of safe, effective and quality essential medicines in the region. Harmonization of regulatory requirements and procedures within the region would lead to a more efficient environment for market access, as well as to allow wider distribution of essential medicines in the region. There is clearly a need to assess potential barriers to harmonization within the SADC region and identify possible strategies to address these.

1.3. Study Aim

The aim of the present study is to identify the perceived_barriers to current medicines regulatory harmonization efforts within the SADC region by stakeholders involved, as well as possible strategies to address the barriers.

1.4. Study Objectives

The objectives of the study are the following:

- To evaluate the current status of medicines regulatory harmonization within the SADC region;
- To identify and explore the perceived barriers to medicines regulatory harmonization of the national regulatory authorities within the SADC region;
- To identify possible strategies and recommendations to address the recognised barriers to regulatory harmonization within the SADC region.

Chapter 2 – Methods

A cross-sectional exploratory study design with qualitative techniques, as well as an inductive-deductive approach, which involved the prior identification of emergent themes as well as the emergence of new themes, was used. In-depth face-to-face interviews with key informants from various stakeholders in the healthcare sector, involving secondary formal qualitative approaches to identify the emergent themes, was utilised initially. This was deemed beneficial in this context, as it assisted in formulating the retrospective hypothesis of existing barriers to medicines harmonization, used later in the cross-sectional study. A study sample consisting of regulatory authorities in the SADC region was used in the cross-sectional study.

2.1. Face-to-Face Interviews

Initially, a series of semi-structured, one-on-one interviews with 4 key interviewees from the SADC Secretariat, the African Medicines Harmonization (AMRH) Initiative and the Southern Africa Regional Programme on Access to Medicines and Diagnostics (SARPAM) was used. The sample used for this was purposive, as senior policy specialists and decision-makers from the relevant institutions were targeted. Inclusion criteria for interviews were key decision makers who had a sound knowledge of medicines regulatory harmonization activities. The number of interviewees was tailored according to the point that data saturation was reached. This occurred when a theme was repeated three to four times and no new codes were formed. Standardized, open-ended questions were used to allow ease of comparison and replication with interviewees.

The following were adhered to during the face-to-face interview:

- A setting with minimal distraction was identified;
- The purpose of the study was explained and queries addressed;
- The format of the interview and expected duration were explained;

- Contact information was provided and consent obtained, as well as explanation that names would be kept confidential, but that geographical location and role in organization may be stated in results.

Biased questioning was avoided and participants were encouraged to lead the interview, defining the content. Controversial questions were left until the end of the interview and factual questions were asked first. At the end of the interview, points reported were summarized and accuracy confirmed with the participant. A neutral, unbiased person with no link to the participants assessed electronic records of interviews conducted. If any bias was suspected, participants could be contacted to ensure objectivity and reconfirm their view. However, this was not necessary, as the interviews were considered to be unbiased.

2.2. Piloting of the Questionnaire

A questionnaire was formulated and adapted using secondary data collected from the face-to-face interviews. Themes derived from the interviews were challenged or confirmed by responses to this questionnaire. The tool was piloted with a group of 6 individuals – 3 research experts who are regularly involved in the design of clinical research studies, 2 members of the Medicines Control Council (MCC), both of whom were regularly involved in harmonization initiatives, and one member of the AMRH Initiative to determine acceptability, validity and reliability of the method. The pilot sample used was chosen out of convenience and where face-to-face or telephonic contact was already established. The questionnaire was assessed for fluidity, ease of use, completeness of parameters used, ability to comprehend key issues, time taken to complete, fairness and lack of bias.

2.3. Distribution of Questionnaire

The questionnaire was designed before the face-to-face interviews, then adapted after the interviews to confirm themes derived from the interviews. The questionnaire was formulated in English, and data collected therefore had a bias towards English-speaking and educated individuals. However, as English is a requirement of all regulatory submissions in the SADC countries, it was assumed that the target population was proficient in English and would therefore respond. Questionnaires were delivered via email to the members of the relevant national medicines regulatory authorities. It was confirmed beforehand that the target population had sufficient Internet connectivity to support communication.

Questionnaires were sent to senior members of all 15 regulatory authorities belonging to SADC, including registrars and deputy registrars. The individuals were contacted using information available on the authorities' websites. If no response was received from the questionnaires within two weeks, reminder emails were sent, with further email follow-up made for two months. If no response was received after two months from submission of the questionnaire, it was assumed that the subject was unwilling to participate.

2.4. Justification for Method Used

A qualitative method was used to identify perceived barriers that exist to medicines regulatory harmonization in the SADC region. Theoretical and analytical codes were identified from repeated ideas, concepts or elements. Codes were grouped into concepts, and then into categories. Mixtures of pre-set and emergent codes were used. Pre-set codes were derived from the literature research conducted and emergent codes were formulated according to word repetitions and indigenous categories.

Unstructured, open-ended questions, as used in the study, provide a framework for response, as well as allow freedom of expression of the respondent in the investigation (64). Using content analysis to draw conclusions, a range of issues that were perceived as impeding regulatory harmonization and improved standards of regulatory control in the SADC region were determined.

TABLE II: Methods and Objectives of the Study

Objective	**Method**
To evaluate the current status of medicines regulatory harmonization within the SADC region; To identify and explore the perceived barriers to medicines regulatory harmonization of the regulatory authorities within the SADC region; To identify possible strategies and recommendations to address barriers to regulatory harmonization within the SADC region.	Interviews conducted; Questionnaires formulated and piloted; Questionnaires evaluated and adjusted then sent out via email; Content analysis.

2.5. Data Analysis

2.5.1. Content Analysis

Content analysis was used, which is the "objective, systematic, and quantitative description of the manifest content of a communication", converting written and verbal information into a quantifiable format (64). Text from open-ended and structured questions was inferred into thematic unit categories for interpretation. Trend analysis was conducted, involving an in-depth analysis of patterns. Saturation points were reached when no new codes were formed. As modest claims were hypothesized, the sample size was small. The sample size did not impact the outcome of the qualitative analysis, as this was determined on point of saturation. Trends were interpreted according to discrete categories and compared

according to country perspective. Levelling of responses according to personal expression was also undertaken.

Saturation points were reached rapidly during the conduct of the study, with most participants alluding to the same thematic concepts of the barriers to SADC harmonization. Although only 47% of the regulatory authorities that were sent the survey responded, it was determined that saturation points had been reached and qualitative analysis was possible.

2.5.2. Data Collection and Analysis Process

In summary, the data collection and analysis processes were as follows:

- Interviews were conducted and information assessed;
- Questionnaires were formulated and piloted to assess fluidity, ease of use, completeness of parameters used, ability to comprehend key issues, time taken to complete, fairness and lack of bias;
- Questionnaires were evaluated and adjusted, then sent out via email;
- Completed questionnaires were collected;
- Content analysis and identifying relevant themes and trends with regards to barriers to harmonization were performed.

2.6. Ethics

Approval to conduct the study was obtained from the University of the Witwatersrand Human Research Ethics Committee 20 April 2015. Written consent was received from participants in the interviews. Written consent was also received from participants in the questionnaire. Consent forms and interview transcripts can be made available on request.

2.7. Limitations

A number of limitations were identified involving the collection of data for the research study. Although all regulatory authorities in the SADC region were approached to complete the survey, only 7 out of the 15 Authorities (47%) responded. Responses received were personal views and did not necessarily reflect the view of the regulatory authorities or organizations. It was found that countries participating in harmonization activities such as Zazibona were most responsive to the questionnaires, while participants from countries where English is not a first language were least responsive.

Chapter 3 - Evaluation of the Current Status of Medicines Regulatory Harmonization

The current status of medicines regulatory harmonization in the SADC region was evaluated from the face-to-face interviews. Using a small but diverse group of individuals involved in regulatory harmonization, from the SADC Secretariat, the AMRH Initiative, SARPAM and members of regulatory authorities, a broad understanding of the current regulatory environment was developed. During the interviews, various concepts emerged repeatedly, regarding the barriers to harmonization. These points became saturated following the piloting and distribution of the questionnaires to the wider regulatory participants.

A trend analysis undertaken from responses to questionnaires and interviews showed participants from the various countries within SADC identifying similar themes, regardless of capacity and years of operation of regulatory authorities, as well as whether the authorities had participated in regional harmonization activities. Although some participants from advanced regulatory authorities only indicated value in convergence rather than complete harmonization at this stage, which may be a more realistic view due to the different capacities of regulatory authorities, all participants were in favour of harmonization, if the identified barriers could be overcome.

Interviewees suggested that regulatory harmonization in the SADC region was "initially… driven by the industry" (Interviewee 3, AMRH Initiative). It was deemed by the industry as easier to submit one registration application to various countries to ensure greater market access. One interviewee involved in SADC harmonization activities at its commencement explained that "for the industry, the earlier their products can come to the market the better and their products can only come to the market on being registered" (Interviewee 1, SARPAM).

Although criticism of the SADC secretariat existed, it was agreed that various advances had been made in the SADC region. A SADC participant stated that "the first [priority] was to develop minimum standards, so [it] developed guidelines for registration and control of medicines. It [is then] up to countries to adopt those guidelines" (Interviewee 2, SADC). According to the interviewee, there has been an agreement to adopt the CTD format by all Ministers of Health in the SADC region.

SADC, with the help of SARPAM, also created a procurement platform - "a database where countries are sharing information… to see how countries are comparing the prices that they are buying at" (Interviewee 1, SARPAM). SADC and SARPAM are also currently developing a pooled mechanism of procuring medicines with the vision to combine the assessment and registration of quality medicines with pooled procurement in order to ensure access to more affordable, safe and good quality medicines. The SADC interviewee indicated that the organization's "aspirations [are] that the region should be able to produce some of the medicines and procure together and ensure these medicines undergo stringent regulatory analysis to ensure that they are safe" (Interviewee 2, SADC).

The Zazibona initiative was viewed by participants from SADC, SARPAM and AMRH Initiative in the face-to-face interview as being a key first step to harmonization. The SADC interviewee stated that it "is up to [the countries participating in the Zazibona initiative… to share… their experiences and we can see how… we can accommodate [them] in a SADC-wide programme" (Interviewee 2, SADC). As one of the drivers of this initiative, a participant from the AMRH Initiative stated that "for the SADC region, we rely heavily on Zimbabwe. Zimbabwe regardless of the economic situation... has retained and maintained the same level of capacity and… has played a very good role in teaching other countries in the region" (Interviewee 3, AMRH Initiative).

One interviewee who has been involved with the Zazibona initiative indicated that it incorporated the harmonization work of "the East African Community as [a]

reference guide for setting up… standards and [in] November/ December [2014] it was officially integrated as a SADC programme" (Interviewee 3, AMRH Initiative). The interviewee went on to say "I totally think the EAC can be used [as a model for SADC harmonization], the reason being is the way that it is structured [in such a way that] takes into account the variations in capacity" (Interviewee 3, AMRH Initiative).

The face-to-face interviews showed that the current status of regulatory harmonization in the SADC region is one in which many barriers exist that must be overcome. The study showed that there is buy-in from the stakeholders involved in medicines regulation within the countries in SADC, but that progress towards harmonization had been slow to date. The Zazibona initiative emerged as a well-supported and successful effort that should be replicated. These themes were discussed through the survey responses in Chapters 4 and 5.

Chapter 4 - Perceived Barriers to Medicines Regulatory Harmonization

A number of barriers to medicines regulatory harmonization in the SADC region emerged through the face-to-face interviews. Through the questionnaire responses that were received, several recurring themes that were identified during the face-to-face interviews were confirmed and reached saturation point rapidly. The barriers that emerged in the questionnaire component of the study are summarised in TABLE III below and explained in detail in this chapter. Responses were tabulated for each theme that emerged from the questionnaires and were simplified for consistency and ease of reference. Completed questionnaire responses are presented in Appendix 3.

TABLE III: Perceived Barriers to Medicines Regulatory Harmonization

Themes	**Contributing Factors**
Governance and Leadership within SADC	Inertia
	Lack of Coordination
	Lack of Prioritization
Capacities of Regulatory Authorities	Limited human resources
	Different levels of development
	Maturity of regulation
	Different levels of expertise
Financial Resources	Different socioeconomic status
	Lack of funds to take part in activities
Political Will	Lack of perceived benefit
Intra-SADC Relationships	Diverse cultures and language
	Different heritage, tradition and cultures
Risk-Benefit Analysis Difference	Each regulator has final decision, with different interpretation and priorities
Legal Framework	Lack of adoption of CTD Format
	Lack of enabling legislation
	Out-dated SADC framework
	Lack of faith in harmonization guidelines

4.1. Governance and Leadership within the SADC Secretariat

4.1.1. Survey Responses

TABLE IV: Barrier of Governance and Leadership

Question	Respondent 8
Strategies to improve harmonization	Building of capacity at the Secretariat

Respondent 8 stated that a possible strategy to improve harmonization would be to build capacity of the SADC Secretariat. This implies that the lack of capacity of the SADC Secretariat to coordinated harmonization activities is a major barrier to SADC harmonization.

4.1.2. Interview Responses

This major theme that was identified as a barrier by some participants involved in harmonization is the apathy or "inertia" of the SADC secretariat due to "protocols and bureaucracy" (Interviewee 2, SARPAM), limiting the progress of the SADC harmonization agenda. One interviewee indicated that the "lack of coordination method of the SADC Secretariat... has really hampered progress in the SADC region" (Interviewee 3, AMRH Initiative).

Interviewees indicated that the SADC secretariat does not prioritise harmonization as a key function and role within the organisation. In the face-to face discussion with a member of the Secretariat, willingness was expressed to support harmonization activities amongst member states once positive results of such initiatives began to emerge. This approach to supporting harmonization was considered more appropriate since "whatever [SADC does is taken] through the process of adaptation and domestication and.. through the Ministerial Technical Committee discussion for them to agree" (Interviewee 2, SADC). Poor cooperation between the SADC Secretariat and governing bodies has been a contributing factor impeding harmonization.

4.1.3. Discussion

It was evident from the face-to-face interviews and questionnaire responses that many countries had been waiting on the SADC Secretariat to create an environment for countries in the region to harmonize. It appears that many countries had become frustrated with the inefficiencies within the SADC secretariat with regards to enabling harmonization activities and using funds designated for harmonization activities efficiently. This is a great concern, as harmonization needs to be encouraged on a SADC level to ensure the participation of all countries.

However, the SADC Secretariat did not see merit in initiating harmonization, as the red tape within the SADC structure would not allow for a quick turnaround of efforts. It envisioned a scenario where the countries themselves would initiate harmonization efforts on their own, and later request the support of the secretariat to facilitate engagement with the wider community within the region. This could result in issues around funding for these efforts, as well as coordination.

4.2. Capacities of Regulatory Authorities

4.2.1. Survey Responses

TABLE V: Capacity Barriers of Regulatory Authorities

Question	Respondent 7	Respondent 8	Respondent 9	Respondent 10
Problems encountered	Gaps between regulatory systems	-	Different levels of capacity	Wide variation of regulatory systems
Major barriers	Different levels of development and maturity	Dependency on external technical and financial support	Difference in capacity levels	Capacity limitations
Number of evaluators	90 Internal 110 External	15 Internal 50 External	11 Internal 9 External	24 Internal 0 External
Drugs registered in 2014	526 Generics 26 NCEs	425 Total	370 Generics 4 NCEs	143 Total

The four respondents listed in TABLE V above belong to regulatory authorities of varying capacities, consisting of between 20 to 200 evaluators and registration of 143 to 552 medicines annually. However, the themes that emerged regarding problems encountered in harmonization attempts and major perceived barriers were similar. Differences and limitations in capacity were common barriers perceived by respondents, a major theme that reached saturation in the research report. Another respondent added that "harmonization can only be discussed with certain SADC countries due to the large gap between the implemented regulatory systems".

4.2.2. Interview Responses

A recurring theme that emerged from the interviews, which was then tested and confirmed in the questionnaire during the survey conducted was that "different

levels of development" and "human resources" (Interviewee 2, SADC) were major barriers to harmonization. Interviewees who had been part of Zazibona activities sited "Different levels of capacity at different regulatory authorities" as a major problem encountered and perceived barriers to harmonization, as well as different "maturity".

One interviewee stated that "infrastructure is not the same, legal issues and laws are different and even in terms of the human resources – most of the experts who are dealing with regulatory issues may not have what is acceptable in terms of standard of training at international level" (Interviewee 2, SADC). It was also noted that the SADC regulatory authorities "need to recognise… that they are at different levels" (Interviewee 1, SARPAM).

4.2.3. Discussion

At a regulatory harmonization workshop held in Washington DC in 2013, the gap between regulatory authority capacities in developed and developing countries was discussed. It was found that these gaps lead to the inability of countries with different capacity to develop at the same levels. It was also found that many harmonization initiatives fail due to a lack of enforced legislation and participation, and that although countries often adopt harmonization in theory, they lack the resources to perform. Without sufficient accountability, harmonization activities are therefore not implemented (50).

It is important that within the SADC context, the different levels of development and maturity of the regulatory authorities is taken into account. For example, Respondent 7's regulatory authority with 200 staff, registering 552 products annually would not necessarily be at the same level as Respondent 10's regulatory authority, with 24 staff, registering 143 products. Although the two regulatory authorities may not be able to fully harmonize at this stage, there are many areas that they may converge on, which are discussed in Chapter 5.

4.3. Financial Resources

4.3.1. Survey Responses

TABLE VI: Financial Resources Barriers

Question	Respondent 9
Problems encountered in harmonization initiatives	Cost of undertaking the activities
Major barriers to harmonization	Funding for joint work
Sources of funding	Government Fees levied by the regulatory authority Industry Donors

Respondent 9 indicated that the regulatory authority they represented received funding from many sources, including the government, fees levied by the regulatory authority, industry and donors. One would assume that receiving funding from a variety of sources would enable adequate funding for harmonization activities. However, the respondent viewed costs and lack of funding as being a major barrier to harmonization.

4.3.2. Interview Responses

Most participants in the study saw lack of financial resources as a major barrier to harmonization. One participant stated that countries "have a huge amount of challenges from infrastructure to human resources [and] financial resources" (Interviewee 3, AMRH Initiative) and that the "variation of the socioeconomic status and the capacity to regulate medicine [is] a big factor that [leads to] either success or failure of harmonization in the SADC region" (Interviewee 3, AMRH Initiative).

4.3.3. Discussion

Regulatory authorities who had undertaken harmonization of regulatory activities cited "cost of undertaking the activities" and funding as major problems encountered and barriers to harmonization. Funding for joint work initiatives was

seen as a major barrier, as some governments do not have the financial means to attend meetings relating to harmonization activities. The recently signed World Bank agreement, as outlined on Page 19 of this report, will hopefully address this constraint as countries would be able to have access to funding for joint work initiatives and meetings.

Funding sources for participating National Regulatory Authorities (NRAs) differed between government, fees levied by the NRA, industry and donors. However, a common theme, independent of funding source, was that finances posed a major barrier to harmonization.

4.4. Lack of Political Will

4.4.1. Survey Responses

TABLE VII: Barrier of Political Will

Question	Respondent 5	Respondent 6	Respondent 8	Respondent 10
Problems encountered in harmonization initiatives	Differing Assessment standards and levels of expertise	Trusting other authorities' decisions	-	Slow progress
Major barriers to harmonization	National pride	-	Lack of understanding of harmonization benefits	-
Participation in training on harmonization guidelines	Yes - WHO and SADC	Yes - WHO and ICH	Yes - WHO	Yes
Involvement in information sharing in SADC	Yes - Zazibona	N/A	Yes - SADC Heads of Agencies forum	Yes
Benefit from SADC Harmonization	Yes	Yes	Yes – quicker registration, information sharing and capacity	Yes

The four respondents listed in TABLE VII above all saw benefit in SADC regulatory harmonization, and had been involved in harmonization activities. However, a common theme that emerged as a barrier to harmonization was trust in harmonization activities and decisions made by other regulatory authorities, which has led to slow progress so far.

4.4.2. Interview Responses

One view emerged that NRAs in some countries like "South Africa... are not willing to work with other countries – they feel like working with other countries is dragging them back...[but] once the new South African Health Products Regulatory Authority (SAHPRA) is operational, South Africa can start looking into beyond its territory" (Interviewee 3, AMRH Initiative). Political will was seen by participants as important because, as one participant stated, "the minute you have country leadership, it instils ownership and ensures sustainability" (Interviewee 3, AMRH Initiative).

4.4.3. Discussion

It was noted by some participants that although the SADC ministers had agreed to use the CTD format and adopt the protocol on harmonization, some countries were more interested in harmonizing than others. There may be many factors influencing this, including limited resources and funding to be able to provide for staff to participate in these activities, as discussed previously.

The perception that some countries have not shown interest in harmonization activities in the past may be due to the fact that these countries may only stand to gain a small amount of time saved through joint registration of medicines and other regulatory issues may take priority for under-resourced regulatory authorities. These countries may not want to neglect their own growth, especially in South Africa with the impending implementation of the new regulatory authority, SAHPRA. South Africa may choose to become an observer for initiatives such as Zazibona in order to provide expertise and build capacity as well as to learn from the process, while not deviating from current standards and practices to which the country adheres.

4.5. Lack of Intra-SADC Relationships

4.5.1. Survey Responses

TABLE VIII: Barrier of Lack of Intra-SADC Relationships

Question	Respondent 4	Respondent 5	Respondent 6	Respondent 8
Major barriers to harmonization	Issues of sovereignty	National pride	Trust building	Language barriers
Benefit from SADC Harmonization	Yes - working sharing to expedite product registration	Yes	Yes	Yes - information sharing and capacity for quicker registration
Most to gain from harmonization	Recognition of work done by other member states Reduce work in country Facilitate learning	Improve on assessment standards and elimination of duplication of work	Knowledge sharing and faster decision-making, leading to diminished back-logs	N/A

The above table displays the responses of four questionnaire respondents, detailing barriers relating to a lack of national relationships between SADC states. While all four respondents saw benefit in SADC harmonization, including reducing their own regulatory workload and reducing backlogs, the respondents saw a lack of trust and national pride, as well as language barriers as contributing to barriers to harmonization.

4.5.2. Interview Responses

It was noted by one interviewee that the EAC was "colonised by the British and Germans… so they had a lot of similarities in terms of culture and language.. [which made it easier] for the countries to work together" (Interviewee 3, AMRH

Initiative). It was noted that in comparison, the SADC region consists of countries with diverse cultures and languages.

4.5.3. Discussion

Diverse cultures and language within the SADC region is potentially a major barrier to harmonization. Although the majority of the region uses English as their main official language, the Democratic Republic of Congo uses French, while Angola and Mozambique use Portuguese. This was seen as a difficult obstacle to overcome and may contribute to communication challenges in harmonization activities in some countries in the region.

Countries within SADC who lack mutual recognition and trade relations are at greater risk of these barriers. These issues evolve from less regional collaboration as compared to the EAC, which has agreements set up to encourage cooperation.

Another issue facing the SADC region and affecting intra-SADC relationships is the perceived low standard of governance and transparency in some countries. Cooperation and mutual recognition has been highlighted as a key factor for cohesion and growth in the region. South Africa contributes the highest Gross Domestic Product in the SADC region and, along with Zimbabwe, is viewed by some as the "political engine" within SADC, but also risks being viewed as taking control and imposing its view on other members of SADC (49).

4.6. Risk-Benefit Analysis and Law Interpretation Differences

4.6.1. Survey Responses

TABLE IX: Barrier of Risk-Benefit Analysis Difference

Question	Respondent 7	Respondent 8	Respondent 10
Problems encountered in harmonization initiatives	Final decision still remains with each regulator	-	Variation in regulatory systems
Major barriers to harmonization	-	Poorly established regulatory systems	Levels of development and systems
Countries decisions are recognized from	PIC/s countries No others within SADC	ICH Countries No others within SADC	Zazibona countries
Registration of products based on registration in other countries	No	No	Yes

Respondent 10, indicated as registering products based on decisions made through the Zazibona initiative, saw the different levels of development of regulatory systems as a barrier to harmonization. Respondent 7 and 8, who both stated that they had not taking decisions from other SADC countries and had not registered products based on any other country's decision, partly due to the barrier of different regulatory systems, echoed this theme.

4.6.2. Discussion

Different risk-benefit decisions and interpretation of legislation may affect the way that regulators in the SADC region make regulatory and product approval decisions and may create a barrier to harmonization. For example, even the interpretation of the AU Model Law may be different according to local needs. One respondent involved in regulatory harmonization activities stated that a

barrier to harmonization was that “the final regulatory decision still remains with each specific regulator.”

At a regulatory harmonization workshop held in Washington DC in 2013, it was found that even under the same legal and scientific frameworks, regulatory authorities of countries prioritise different areas of risks and benefits during medicine regulation (50). The priority needs of the local population and epidemiology within a particular country may influence a regulator’s decision to approve or reject a medicine based on its efficacy and side effect profile. An example that was presented at the above-mentioned workshop included the withdrawal of approval of Avastin for breast cancer by the FDA due to a high side effect profile and a low proof of efficacy. However, Avastin is available in other countries for this indication, raising concerns from the public and potentially reducing trust in the regulator’s decision. Regulators need to make risk-benefit decisions with “balance and perspective” (50).

4.7. Different Guidance Documents and Legal Frameworks

4.7.1. Survey Responses

TABLE X: Barrier of Different Guidance Documents and Legal Frameworks

Question	Respondent 4	Respondent 5	Respondent 7	Respondent 9
Problems encountered in harmonization initiatives	-	Legislation differences	SADC Guidelines is out-dated	-
Major barriers to harmonization	Difference in the legal frameworks and application format	Legislation differences	-	Different guidance documents
Priority areas for harmonization	Format of Applications	-	Format of Applications	Format of Applications
In what year was your legislation created	1929 (undergoing update)	1965	1965	2013

The respondents listed in TABLE X above indicated legislation that was created from as far back as 1929 to as recently as 2013, with a recurring theme that harmonized legislation should include that of format of applications. The four respondents saw major barriers being caused by differences in legislation and guidelines that needed updating.

4.7.2. Discussion

The New Partnership for Africa's Development (NEPAD) undertook an analysis on regulatory agencies in Africa and found that although most countries had laws to enable regulation of medicines, most of these were out-dated and not comprehensive enough (62). This theme was repeated in the research study, in which participating countries' medicine legislation dated as far back as 1929,

although this legislation is currently undergoing an update. All participating countries indicated that their legislation makes provision for the establishments of a NRA, which has the power to carry out inspections of pharmaceutical products and practices as well as the responsibility to deal with non-compliant products or companies.

To address this, the AU Model Law was developed to create a foundation on which regulatory authorities could build their legislation. This law was approved by AU Ministers of Health and is aimed at addressing issues that enable harmonization, including allowing information sharing and recognition of decisions by other regulatory authorities (65).

The NEPAD situational analysis was confirmed by the findings in this study, where most respondents indicated that their legal frameworks currently do not allow for information sharing or harmonization in the SADC region. This would be a major factor that requires change if harmonization in the SADC region is to occur.

The use of different guidance documents and legal frameworks was seen as a major barrier to harmonization. This includes the fact that although the Ministries of Health within SADC have agreed to adopt the CTD format, not all countries within SADC have implemented the format completely. This difference in format is a major barrier, as pharmaceutical companies are forced to submit different formats to different countries and joint evaluation is extremely difficult.

An on-going challenge is the ability to adapt requirements to each country's environment. This is a major barrier which must be resolved as lack of faith in the SADC guidelines could lead to countries becoming resistant to adopting them, leading to a lack of harmonization. For example, another respondent who cited that the guidelines were out-dated added that WHO guidelines addressing harmonization were used instead of the SADC guidelines. A lack of faith in the

guidelines is a major issue as, without adoption of these guidelines as a foundation, harmonization in the region will be almost impossible.

Chapter 5 - Possible Strategies and Recommendations to Address Barriers

A number of possible strategies to address identified barriers to medicines regulatory harmonization emerged in the face-to-face interviews, as well as the questionnaire responses. These are summarised in TABLE XI below and explained in this chapter. Questionnaire responses were tabulated for each theme that emerged and were simplified for consistency and ease of reference. Complete questionnaire responses are presented in Appendix 3.

TABLE XI: Strategies and Recommendations to Address Barriers

Themes	**Contributing Factors**
EAC and Zazibona as Models	Reference guide for standards
	Variations in capacity of regulators
	Tanzania experience
Format Harmonization (CTD) and Model Law Adoption	Information sharing and transparency
	Cooperation
	Market access for industry
	Easier work sharing initiatives
Redirect Focus	Scientific and technical matters over legislation
	Prioritise information and work-sharing
Regulatory Initiatives	Power of decision making
	Coordinate outside of SADC secretariat
World Bank Agreement	Funding for harmonization
	SADC harmonization goals
Capacity Development	Centres of Regulatory Excellence
	Harmonized Curricula
Convergence over Harmonization	API and Biowaiver requirements
	Post-registration amendments
	International Generic Drug Regulators Pilot
Global Regulation	Globalisation of industry
	Capacity building and transparency

5.1. EAC and Zazibona as Models

5.1.1. Survey Responses

TABLE XII: Strategy using EAC and Zazibona

Question	Respondent 4	Respondent 8	Respondent 10
Strategies to improve harmonization	Work-sharing such as Zazibona	Joint assessments and inspections as pilot projects	Moving with a subset of countries that have similar systems
Perceptions of the Zazibona initiative	Great initiative to speed up market authorization, minimization duplication and allow learning	Stringent regulatory requirements and information sharing, providing capacity building and reducing workload Reduction of substandard medicines	Allows sharing of information and collaboration – full participation

Various respondents, including three respondents listed in the table above, saw work-sharing and joint assessments through collaboration efforts such as the Zazibona initiative as good strategies to improve harmonization. One respondent in the Zazibona initiative described it as a "good way of sharing work, trust building and capacity building" and that continued participation would result in "continued capacity building and work sharing. It would also lead to recognition of work by other countries including report sharing and decisions." Another respondent indicated that the initiative addressed one of the barriers to SADC harmonization, in that strict regulatory standards were upheld and capacity was improved through training aimed at regulators with a lower level of capacity. Even respondents that were not, at the time of the study, part of the Zazibona initiative expressed support and indicated the value that they saw in all SADC member states being part of the initiative.

5.1.2. Interview Responses

The interviewee from the AMRH Initiative stated that lessons might be taken from the success of the EAC, in that, with the will of member states, harmonization will be possible. The AMRH Initiative respondent indicated that the organization would like to use the EAC model for implementation in the wider African community and that, although each region comes with a different set of challenges, the basic framework for harmonization used in the EAC may be replicated.

Another interviewee indicated that "the EAC has done a lot in terms of putting the structures that will drive the process" (Interviewee 1, SARPAM) and also indicated that SADC, although more advanced in implementing the CTD format, would be able to model their harmonization efforts on the EAC.

5.1.3. Discussion

Countries who had not participated directly in the Zazibona initiative saw a great deal of importance in the initiative and indicated support for it, especially with regards to the information sharing aspects. All participants in the study expressed support for the Zazibona initiative, with the general consensus being that "it has served as good way of sharing work, trust building and capacity building". This support for the initiative indicated enthusiasm within SADC for harmonization initiatives and that a wider adoption of the Zazibona principles would be welcomed.

There is a unique opportunity for SADC to use the experience that Tanzania has gained in the EAC initiative. Being a part of both the SADC and EAC region, Tanzania has obtained a wealth of knowledge from the harmonization activities in the relatively successful EAC harmonization initiative. With about 425 registrations annually, the Tanzanian regulatory authority is relatively advanced. Although it was stated that the Tanzanian medicine legislation does not incorporate the SADC Protocol on Health currently, there is provision for information sharing and international cooperation within the legislation. Tanzania

has shown political will in participating in the SADC Heads of Agencies Forum, as well as participating in Zazibona joint assessments. Tanzania sees SADC harmonization as beneficial to "facilitate information sharing and hence facilitate quick registration of essential medicines".

5.2. Format Harmonization (CTD) and Model Law Adoption

5.2.1. Survey Responses:

TABLE XIII: Strategy of Format Harmonization and Model Law Adoption

Question	Respondent 4	Respondent 6	Respondent 9
Strategies to improve harmonization	Harmonization of Regulatory Framework Harmonization of Application Format	Formal systems need to be implemented and controlled	Adoption of regional guidelines by all countries
Incorporation of the SADC Protocol on Health in your legislation	Yes	No	Yes

The three respondents listed in TABLE XIII indicated that regional guidelines, such as the AU Model Law, would need to be adopted to improve harmonization. Only two of the three of these listed respondents indicated that the SADC Protocol on Health was part of their country's medicines legislation, which would need to be incorporated for SADC harmonization to occur. All except one respondent identified "format of applications" as a priority of harmonization.

5.2.2. Interview Responses

One interviewee noted that the "thing that is... going to help [harmonization] is the Model Law" (Interviewee 1, SARPAM). A SADC interviewee stated that "[SADC] harmonization processes in as far as medicines are concerned are governed by what is found in the Protocol on Health" (Interviewee 2, SADC). However, not all of participants in the survey indicated that their medicines legislation included the SADC Protocol on Health.

Another interviewee involved in harmonization activities indicated that there is a big drive from industry for application format harmonization as it is "easier for

the industry to submit their dossier straight on one set of requirements", especially for GMP inspections and application formats (Interviewee 3, AMRH Initiative).

5.2.3. Discussion

The adoption of the AU Model Law will enable SADC regulatory authorities to be able to share information between countries and adopt the decisions of other regulators within SADC. Although medicines legislation is needed to be country-specific to ensure sovereignty and to deal with local challenges, the basis of the law should allow for harmonization.

Although SADC countries have agreed to adopt the CTD format for registration applications, its implementation is still limited in some countries. Adopting the format will enable pharmaceutical companies to submit applications to many countries within SADC, increasing market access and leading to wider availability and accessibility of medicines. Adopting the CTD format will also enable technical working groups to coordinate work-sharing initiatives easier and more efficiently.

5.3. Redirect Focus of Harmonization

5.3.1. Survey Responses

TABLE XIV: Strategy of Redirecting Focus

Question	Respondent 5
Strategies to improve harmonization	Concentrate on scientific and technical matters in terms assessment of product applications and inspections

6 out of the 7 survey respondents listed "technical regulatory requirements" as a priority area for harmonization. Respondent 5 stated that the focus on harmonization should be on "scientific [and] technical matter" instead of "legislative frameworks and registration processes". Due to the different capacities of the SADC regulatory authorities, another respondent stated "detail to which each country should decide to go as far as regulation of medicines is concerned will depend on level of development, staffing available and facilities available".

5.3.2. Interview Responses

The theme emerged that with successful harmonization, highly developed regulatory authorities will be able to empower less developed ones. As one participant during a face-to-face interview indicated, "that's what we want to see – countries helping one another" (Interviewee 3, AMRH Initiative).

5.3.3. Discussion

SARPAM at a regulatory conference in 2013 discussed that regulatory harmonization should first focus on "low-hanging fruits such as information and work sharing" (65). This recurring theme that emerged in the study included the view to focus on harmonization of technical requirements rather than broader legislation. Although it is hoped that harmonization in the SADC region could lead to a central regulatory authority (see TABLE I on Page 16), until capacity is increased through initiatives like establishing Regional Centres of Regulatory Excellence (RCOREs), the first step to harmonization would be convergence through information sharing.

5.4. Regulator Initiatives outside of the SADC Secretariat

5.4.1. Survey Responses

TABLE XV: Strategy of Regulator Initiatives

Question	Respondent 5	Respondent 7
Perception of the Zazibona initiative	Good model that all SADC states should adopt	Support the initiative
Strategies to improve harmonization	-	Strategize according to country maturity

TABLE XV above illustrates the support that respondents showed for the Zazibona initiative, which, as detailed on Page of 19 this report, was constructed outside of the SADC Secretariat's control. Participants in Zazibona took the initiative to coordinate harmonization activities without the SADC Secretariat, allowing greater flexibility to work according to country maturity and ability, as suggested by Respondent 7 as a strategy to improve harmonization.

5.4.2. Interview Responses

To address the barrier of lack of coordination by the SADC Secretariat, two participants who were part of regulatory harmonization initiatives indicated that for SADC harmonization to occur, countries would have to take the initiative to coordinate their own meetings and activities, while still falling under the SADC umbrella. One interviewee explained that "if you want anything to move as a region, it makes it a lot easier once it is moved from SADC… [Efforts should be coordinated] through SADC but [countries should not have] to wait for their go-ahead… so there is need to shift the power of decision making" (Interviewee 1, SARPAM). The interviewee also added that regulatory authorities "are not at the same level and when it comes to expertise... they can benefit from those countries that have" (Interviewee 1, SARPAM).

The SADC interviewee confirmed that this is an ideal situation and that SADC "encourage[s] countries to partner amongst themselves. They should be free to

recognise the strengths of each-other and share information on their own using their levels of sovereignty and only using [SADC] to coordinate where necessary" (Interviewee 2, SADC).

Regarding the success of the Zazibona initiative, the SADC interviewee indicated that "it is up to them now to share with us their experiences and we can see how then we can accommodate it in a SADC-wide programme… So the way forward is simply for countries to be able to have joint initiatives and secretariat facilitates and that's what brings integration in the end" (Interviewee 2, SADC).

5.4.3. Discussion

This strategy of regulatory authorities initiating harmonization activities would be useful in addressing the barrier of lack of leadership within the SADC Secretariat. It would result in a higher chance of sustained participation, as countries would have a sense of ownership of the harmonization activities and not have these imposed by the Secretariat. Activities could also be tailored in accordance with specific country needs of those participating. Moving with a subset of countries with similar goals and abilities would achieve favourable results, as shown with the Zazibona initiative.

It is also imperative to involve the pharmaceutical industry in the process of harmonization, as the regulatory authority and industry should work together to achieve a common goal. Medicines harmonization activities should be adapted by regulators according to local circumstances.

5.5. Capacity Development

5.5.1. Survey Responses

TABLE XVI: Strategy of Capacity Development

Question	Respondent 7	Respondent 8	Respondent 9	Respondent 10
Benefit of Zazibona	Information sharing	Information sharing and capacity building	Continued capacity building and work sharing	Information sharing
Strategies to improve harmonization	Resources, skills, expertise and political will	Establish Regulatory Authorities in all countries	Training centres Identifying lead experts	Capacity building
Number of evaluators	90 Internal 110 External	15 Internal 50 External	11 Internal 9 External	24 Total

TABLE XVI above indicates that, regardless of number of evaluators in a regulatory authority, capacity building was seen as a key strategy needed to improve harmonization. As respondents listed in TABLE XVI indicated, this may be done through the Zazibona initiative, which enables information sharing.

One participant in this study indication that "no strategies developed by any outsider could be implemented by any NRA in SADC if the necessary resources, skills, expertise and political will are not present." Respondents reiterated the need to "build human resource capacity within Member States" and that the "establishment of training centres and modules for NRA technical staff" would help to enable harmonization. These themes were repeated constantly and reached saturation quickly.

5.5.2. Interview Responses

An interviewee from the AMRH Initiative stated that to increase capacity, countries should establish RCOREs. "The idea behind this is that it helps you to

help countries to work together through a training programme - for example we have started with it for the East African Community. And it is through that we are able to first and foremost build trust among the regulators themselves but also build capacity through work-sharing" (Interviewee 3, AMRH Initiative).

5.5.3. Discussion

A key strategy to address the issue of regulatory capacity in SADC is the establishment of RCOREs through the AMRH Initiative. For example, in January 2016, a bill to amend the Medicines and Related Substances Act 101 of 1965 was approved and signed into law that will lead to the establishment of the South African Health Products Regulatory Authority (SAHPRA), which will be independent of the South African Department of Health, will manage its own finances through retention of fees and will have the required internal regulatory capacity with a lower reliance on external experts. The issue that South Africa now faces is how to rapidly develop evaluator skills that are a major requirement for SAHPRA to function well. To address this, the country is undergoing an exercise to establish an Institute for Regulatory Sciences (IRS) in order to develop human resources to strengthen internal capacity required under the new SAHPRA framework, as well as to support regulatory capacity building within the wider SADC region. The IRS has undergone a pilot phase in which technical staff from the current regulatory authority, the Medicines Control Council, industry and other sectors of healthcare and science were successfully trained to be evaluators (65).

The SADC Protocol on Health proposes "Centres of Excellence" which would allow for pooled resources and increase in capacity for member states. There is also a focus on reduction of counterfeiting, improving quality management and GMP (24). The AMRH Initiative aims to establish "harmonized curricula". It is developing modules to be included in the curricula that should be adapted to meet the specific needs of the various SADC countries. This will be a big step in addressing the lack of regulatory capacity in the SADC region (65).

5.6. Convergence over Harmonization

5.6.1. Survey Responses

TABLE XVII: Strategy of Convergence over Harmonization

Question	Respondent 7	Respondent 9
Benefit from harmonization	No - Convergence would be more useful	-
Strategies to address harmonization	Strategies are developed by each regulator based on in country maturity	Establishment of platform for secure information sharing

It was also suggested for regulatory authorities to "mov[e] with a [group] of countries that have similar systems" and that "strategies [should be] developed by each regulator based on in country maturity" to achieve harmonization. One respondent stated that "convergence between NRAs would be a more useful tool within SADC than harmonisation" and that total harmonization would not be possible. The respondent indicated that convergence of guidelines and information sharing would be a more useful activity in the region.

5.6.2. Interview Responses

A SADC interviewee stated that "member states that are well-developed should not stop and wait for others – they should go on but should allow others to develop as well. So member states will move at their own levels but.. at the end of it all, we have harmony" (Interviewee 2, SADC). The participant also indicated that the "detail to which each country should decide to go as far as regulation of medicines is concerned will depend on level of development, staffing available, facilities available and the policies and political orientation" (Interviewee 2, SADC).

Another interviewee indicated that harmonization efforts should aim for "standardization" but that "that's a pie in the sky [and it is] better to talk about

convergence – coming together to an agreement" (Interviewee 1, SARPAM), as the interviewee saw this as a more realistic scenario.

5.6.3. Discussion

Convergence has a broader view than harmonization, focusing on the practicality of harmonization, rather than the standards and formats involved. The responses received from the more advanced regulatory authorities implied that these countries saw more value in convergence at this stage, in order to open the door to SADC harmonization but not at the cost of global harmonization standards and practices. These countries, who had surpassed minimum standards set out for harmonization, may be able to provide guidance to other less developed regulatory authorities through harmonization initiatives as "observers" rather than full participation, which may be viewed as being too time-consuming.

In order to address the high demand placed on regulatory authorities with generic medicines approval, a group of regulators have launched the International Generic Drug Regulators Pilot (IGDRP), aimed at regulatory convergence and cooperation. Results of the pilot will inform decisions on establishing a more permanent information and work-sharing arrangement as part of broader international efforts related to regulation of medicines. The success of the initiative will require the support of industry as well as other stakeholders interested in promoting access to affordable, quality generic medicines (66).

Regulatory authorities from Australia, Brazil, Canada, the EU, the Republic of Korea, Singapore, Switzerland and the United States as well as the WHO (being the secretariat of the pilot) met in Ottawa in October 2011 to explore opportunities for collaboration. It was recognised that information sharing is a key area of regulatory convergence, including the need to establish electronic platforms for non-confidential data and secure platforms for exchange of confidential data (66).

It was also recognised that industry participation would be key in ensuring regulatory convergence, as applications for medicines registration would need to

be filed with a number of regulatory authorities. A possible barrier to this in the SADC region would be that different regulatory authorities currently have different requirements for Active Pharmaceutical Ingredient (API) quality. With South Africa recently increasing requirements relating to approval of API sources, the other countries in SADC would be required to increase API quality controls. The industry may not be interested in applying for marketing authorisation in countries that have stricter controls than others, unless there is attractiveness of high market demand for the medicine.

At the above-mentioned meeting of regulatory authorities, a higher level of regulatory control and standards was anticipated to be the end results of convergence. An issue that was seen as a barrier is the risk of divergence when post-registration amendments are submitted separately to each authority. The complexity in establishing a collaborative review system was acknowledged, but it was seen that benefits would outweigh the risks (66).

A formal governance structure and terms of reference were first developed, followed by operating procedures and definitions. It was decided to focus on generics before moving to biosimilars at a later stage. Convergence on requirements for API master files and biowavers is needed if SADC convergence is to occur (12).

There is going to be a high level of collaboration between the IGDR and the WHO Prequalification Programme to align requirements under IGDR jurisdictions. It is suggested that the SADC region also aligns with the WHO Prequalification Programme. Most participants in the study indicated that their respective countries had been involved in the WHO Prequalification Programme. South Africa has recently joined the IGDR and thus may bring this expertise to SADC. If regulatory requirements are aligned with the ICH, such as with the IGDR, it will be a possibility to converge with international organizations. This in turn will lead to even wider market accessibility and cheaper generic prices. The close integration of the regulatory authorities involved in the Zazibona initiative

with the WHO Prequalification Programme is a positive step to integrating with WHO and thus international standards (66).

It is suggested that the EU's Decentralised Procedure be used as an information sharing method for third part Regulatory Authorities. Consent is received from the applicant to share confidential information between the authorities (66). The mechanisms for scientific opinion formed by the EMA with the WHO on products intended for use outside of the European Union, as discussed on Page 10 of this report, may also be used for this purpose (34).

Chapter 6 – Conclusion

The purpose of the research was to evaluate the current states of medicines regulatory harmonization within the SADC region, as well as perceived barriers to harmonization and strategies to address these.

It was found that the current state of medicines regulatory harmonization is one in which specific countries interested in harmonization are beginning to evolve best practices and convergence on registration issues. There appears to be a great deal of enthusiasm towards medicines regulatory harmonization from most of the regulatory authorities in the SADC region, regardless of size and capacity of the authorities. However, harmonization progress has been slow. The priority would be for countries to first adopt minimum standards before harmonization can be undertaken.

Through the face-to-face interviews and questionnaire responses, a number of barriers to harmonization were identified and strategies to address these were suggested. The study showed that barriers to SADC regulatory harmonization perceived by participants include governance and leadership within the SADC secretariat, with red tape hindering progress of discussions under the SADC umbrella and forcing countries to create their own harmonization initiatives. Capacities of regulatory authorities was a major barrier identified, with the number of staff and products registered annually differing greatly between SADC countries. A lack of financial resources to undertake harmonization activities was noted as a barrier. Lack of political will to commit and follow through with activities and weak intra-SADC relationships due to diverse cultures and languages spoken in the SADC region were noted. Along with this, risk-benefit analysis differences as well as different guidance documents and legal frameworks were major perceived barriers.

Strategies to address these barriers that emerged from the study included using EAC and Zazibona initiatives as models for harmonization activities, especially

with regards to information sharing. It was suggested that adoption of the CTD format be prioritized, as well as that the AU Model Law ~~adoption~~ be adopted by all SADC member states in order to allow technical working groups to co-ordinate initiatives easier. It was suggested that the focus of regulators be upon information sharing initiatives as a first step to harmonization. The lack of coordination from the SADC secretariat has led to the need for regulators to take initiative and work outside of the SADC on harmonization activities. Capacity development through the establishment of RCOREs is imperative for harmonization to occur. and funding through the World Bank agreement.

Harmonization in the SADC region would mean a more efficient and streamlined system of dialogue between countries, encouraging a common regulatory language, best practices and adaptation to the increasing globalization of the pharmaceutical industry. However, it was suggested by participants in this study that the focus of harmonization activities needs to be redirected and that convergence should be achieved before harmonization. This would mean a more practical approach to allow for different capacities of regulators in the region, as well as other barriers highlighted in the research. As it stands, there is insufficient capacity for SADC to completely harmonize its medicines regulation. It is therefore suggested that countries converge their regulatory activities and gradually move towards complete harmonization in the SADC region, and eventually in Africa as a whole in the future.

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Appendix 1 – Table of Themes and Contributing Factors

Topic	Themes	Categories
Barriers to Medicines Regulatory Harmonization	Governance and Leadership within SADC	Inertia
		Lack of Coordination
		Lack of Prioritization
	Capacities of Regulatory Authorities	Limited human resources
		Different levels of development
		Maturity of regulation
		Different levels of expertise
	Financial Resources	Different socioeconomic status
		Lack of funds to take part in activities
	Political Will	Lack of perceived benefit
	Intra-SADC Relationships	Diverse cultures and language
		Different heritage, tradition and cultures
	Risk-Benefit Analysis Difference	Each regulator has final decision with different interpretation and priorities
	Legal Framework	Lack of adoption of CTD Format
		Out-dated SADC framework
		Lack of faith in harmonization guidelines
		Lack of enabling legislation
Strategies to Address Barriers	EAC and Zazibona as Models	Reference guide for standards
		Variations in capacity of regulators
		Tanzania experience
	Format Harmonization (CTD) and Model Law Adoption	Information sharing and transparency
		Cooperation
		Market access for industry
		Easier work sharing initiatives

	Redirect Focus	Scientific and technical matter over legislation
		Prioritise information and work-sharing
	Regulatory Initiatives	Power of decision making
		Coordinate outside of SADC but under umbrella
	World Bank Agreement	Funding for harmonization
		SADC harmonization goals
	Capacity Development	Centres of Regulatory Excellence
		Harmonized Curricula
	Convergence over Harmonization	API and Biowaiver requirements
		Post-registration amendments
		International Generic Drug Regulators Pilot
	Global Regulation	Globalisation of industry
		Capacity building and transparency

Appendix 2 – Questionnaire

Barriers to Medicines Regulatory Harmonization Questionnaire

Instructions: For open responses, write the response in space provided. For Yes/No or questions with options, please tick the appropriate box.

Respondent Details Name: _____ Designation: _____ Organization: _____ Date: _____	
1	Does your country have specific legislation and supporting regulations for the registration, regulation and control of medicines and health products? Yes ☐ No ☐
2	In which year was the legislation first promulgated and when was it last amended? • Created: _____ Last amended: _____
3	Does the medicines legislation: • Make provision for the establishments of a National Regulatory Authority (NRA)? Yes ☐ No ☐ • Have a definition for a medicinal product, a medical device, in-vitro diagnostic (IVD) or other category of product? Yes ☐ No ☐ • Give the NRA the power to carry out inspections of pharmaceutical products and practices? Yes ☐ No ☐ • Give the NRA the power and responsibility to deal with non-compliant products or companies? Yes ☐ No ☐
4	Does the NRA conduct: • Registration of medicines? Yes ☐ No ☐ • Inspections of manufacturing sites? Yes ☐ No ☐
5	Are regulatory activities organized and performed at a central level of the country? Yes ☐ No ☐ What was the total number of drugs registered in 2014: • Generics: • New Chemical Entities:

6	What is/are the source/s of funding for the NRA (please tick all that apply): ☐ Government ☐ Fees levied by the NRA ☐ Industry ☐ Donors ☐ Other (please specify) _____
7	Does the legislation incorporate the objectives of the SADC Protocol on Health Yes ☐ No ☐
8	Is there provision in your country's legal framework for (please tick all that apply): ☐ Harmonization in the SADC Region ☐ International Cooperation ☐ Information Sharing
9	Does the NRA have cooperative agreements/ Memoranda of Understanding (MOU) with other NRAs? Yes ☐ No ☐ Please Specify:_____
10	How many evaluators does the NRA employ: • Internally: _____ • Externally: _____
11	Has the NRA participated in training on the WHO-Prequalification, ICH, SADC or other guidelines? Yes ☐ No ☐ If Yes, please specify: _____
12	Does your country participate in activities involving (please tick all that apply): ☐ Issuing of CPP certificates following a documented procedure ☐ PIC/s inspections ☐ WHO External Quality Assurance Assessment Scheme (EQAAS) ☐ WHO Drug Safety Monitoring Programme ☐ INCB's international monitoring operations on control of Narcotics and Psychotropic Substances and their Precursors
13	Has the NRA been involved in Regulatory Harmonization activities or information sharing with other SADC countries (please specify) – working groups, forums: Yes ☐ No ☐

14	If the NRA has been involved in Regulatory Harmonization activities, what problems were encountered and how were they resolved, if applicable? • _____ • _____ • _____ • _____ • _____
15	Do you think that your country and other SADC countries would benefit from Regulatory Harmonization within the SADC Region? Your country: Yes ☐ No ☐ Please expand: _____ Other SADC countries: Yes ☐ No ☐ Please expand: _____
16	What do you think your country will gain most from harmonization, if applicable? _____
17	What would you consider to be priority areas for harmonization, in your opinion: ☐ Inspections ☐ Law enforcement activities ☐ Format of applications ☐ Structure of Regulatory Authority ☐ Technical regulatory requirements ☐ Other (please specify)_____
18	Which countries do you recognize and/or uses regulatory decisions, reports (inspection, evaluation, vigilance), guidance or information from • Within SADC: _____ • Outside of SADC: _____
19	Have you registered products based on registration in other countries: • Within SADC?: Yes ☐ No ☐ If Yes, specify:_____ • Outside of SADC?: Yes ☐ No ☐ If Yes, specify:_____

20	What are your perceptions or experiences of the Zazibona initiative? _____ _____
21	How do you think your country could benefit from the initiative? _____ _____
22	What do you perceive as the major barriers to harmonization in the SADC region? • _____ • _____ • _____ • _____
23	What strategies are needed to improve regulatory harmonization in the SADC Region? • _____ • _____ • _____ • _____

Any other comments:

_____

Thank you for your participation!

Appendix 3 – Questionnaire Responses

Questionnaire Responses

	Question		Swaziland - FF (Respondent 4)	South Africa - DM (Respondent 5)	South Africa - AK (Respondent 6)	South Africa - JG (Respondent 7)	Tanzania - SK (Respondent 8)	Zambia - ZM (Respondent 9)	Zimbabwe - LG (Respondent 10)
1	**Does your country have legislation and supporting regulations for the registration, regulation and control of medicines and health products?**		Y	Y	Y	Y	Y	Y	Y
2	**In which year was legislation:**	**Created**	1929	1965	1965	1965	2003	2013 (repealed 2004)	1969
		Last Amended	In parliament for repeal	2003	2014	2015	N/A	N/A	2001
3	**Does the medicines legislation**	**Make provision for the establishments of NRA**	Y	Y	Y	Y	Y	Y	Y
		Have a definition for a medicinal product, IVD etc	Y	Y	Y	Y	Y	Y	Y
		Give the NRA the power to carry out inspections	Y	Y	Y	Y	Y	Y	Y
		NRA power and responsibility to deal with non-compliance	Y	Y	Y	Y	Y	Y	Y
4	**Does the NRA conduct**	**Registration of medicines**	N	Y	Y	Y	Y	Y	Y
		Inspections of manufacturing sites	N	Y	Y	Y	Y	Y	Y
5	**Are regulatory activities organized and performed at a central level of**		Y	Y	Y	Y	Y	Y	Y
	total drugs registered 2014	**Generics**	0	400	-	526	425	370	143 TOTAL
		NCEs	0	26	-	26	-	4	
6	**What is/are the source/s of funding**	**Government**	Y	Y	Y	Y	Y	Y	N
		Fees levied by the NRA	N	Y	N	N	Y	Y	Y
		Industry	N	N	N	N	Y	N	N
		Donors	N	N	N	N	Y	Y	N
		Other	N	N	N	N	N	N	N
7	**Does the legislation incorporate objectives of SADC Health Protocol**		Y	N	N	Y	N	Y	-
8	**Is there provision in your country's legal framework for**	**Harmonization in SADC**	Y	N	N	N	N	Y	N
		International Cooperation	Y	N	N	Y	Y	Y	N
		Information Sharing	Y	N	N	Y	Y	N	N

9	**Does the NRA have cooperative agreements/ Memoranda of Understanding (MOU) with other NRAs**		N	Y - Swissmedic	Y - Swissmedic and MHRA	Y - SwissMedic; Switzerland, USFDA; USA, MHRA ;United Kingdom	Y - In the framework of Harmonization within East African Community	N - But have working relationship with Zimbabwe, Botswana and Namibia under the ZAZIBONA initiative	N
10	**How many evaluators does the NRA employ**	**Internally**	2	12	-	90	15	11	24
		Externally	-	22	-	110	50	6 from other department within institution, 3 from outside	0
11	**Has the NRA participated in training on the WHO-Prequalification, ICH, SADC or other guidelines**		Y - Ministry participates in the development of SADC guidelines, SADC and ICH trainings in GMP and GCP	Y - WHO Pre-Qualification and SADC	Y - WHO and ICH	Y - [WHO-Prequalification, ICH, SADC]. SADC Guidelines however found to be outdated and no longer in line with international best practises	Y - Prequalification of Medicines Programme	Y - WHO prequalification annual training, WHO organised training workshops on dossier review, SADC organised workshops on dossier evaluation.	Y
12	**Does your country participate in activities involving**	**Issuing of CPP certificates**	N	Y	Y	Y	Y	Y	Y
		PIC/s inspections	N	Y	Y	Y	N	N	N
		WHO EQAAS	N	N	N	Y	Y	Y	Y
		WHO Drug Safety Monitoring Programme	Y	N	N	Y	Y	Y	Y
		INCB	Y	Y	Y	Y	Y	Y	Y
13	**Has the NRA been involved in Regulatory Harmonization activities or information sharing with other SADC countries**		Y - take part in the SADC Regulators Forum and ICH RHI and ICH International Pharmaceuticals Regulators Forum (IPRF)	Y - Initially yes, but now only as an invited observer at ZAZIBONA	-	Y - ZAZIBONA work sharing initiative. All WHO Harmonization initiatives and workshops	Y - SADC Harmonization Initiative-Heads of Agencies forum	Y	Y

14	**If the NRA has been involved in Regulatory Harmonization activities, what problems were encountered and how were they resolved, if applicable**		The challenge is that the country has not started registering products coming into its market, only listing has been done thus far, so the training and skills gained and not be implemented immediately. The new Medicines and Related Substances Control Bill once enacted provided for the registration of medicines and the establishment of a NMRA	• Legislation differences • Differing Assessment standards • Perceived levels of expertise • Registration processes	• Trust • Relying on the decisions made by another regulatory authority • Application of harmonization strategies (1st world countries vs. 3rd world countries)	• SADC Guidelines is outdated. Decision then taken to use WHO Guidelines which address the same topic • Harmonization can only be discussed with certain SADC countries due to the large gap between the implemented regulatory systems of the RSA Regulator versus those of some of our SADC colleagues. • The final regulatory decision still remains with each specific Regulator.	• Timely National registration of the products after joint assessments • Release of regulatory officials to participate in joint activities. The problem was resolved by recruitment of National Medicines Regulatory Officers in all NMRAs	• Cost of undertaking the activities • Different levels of capacity at different regulatory authorities	• Slow progress • Wide variation of the countries with respect to regulatory systems
15	**Do you think that your country and other SADC countries would benefit from Regulatory Harmonization within the SADC Region**	**Your country**	Y - The country would not have to reinvent the wheel but can recognize the work done by other member states in the region	Y	Y	N - Convergence between NRA would be a more useful tool within SADC than harmonisation	Y - Will facilitate information sharing and hence facilitate quick registration of essential medicines	Y- It would reduce duplication of work thereby reducing on time it takes to processes application. Each Agency could benefit from the expertise and skill that may be present in other agencies.	Y
		Other SADC countries	Y - Country can benefit from working sharing such as joint dossier evaluation and joint inspections to expedite product registration in their member states	Y	Y	N - Convergence between NRA would be a more useful tool within SADC than harmonisation	Y - Other countries would benefit from current regulatory capacity in Tanzania	Y - it would serve as a capacity building process	Y
16	**What do you think your country will gain most from harmonization, if applicable**		It will facilitate recognition of work done by other member states and reduce work in	Improve on assessment standards and elimination of duplication of work	Harmonization has many benefits including knowledge sharing,	N/A	-	• Work sharing • Skills development • Confidence building	Easier to share information and to collaborate
17	**What would you consider to be priority areas for harmonization, in your opinion**	**Inspections**	Y	Y	Y	N	Y	Y	N
		Law enforcement	N	Y	N	Y	Y	N	N
		Format of applications	Y	N	Y	Y	Y	Y	Y
		Structure of NRA	N	Y	Y	N	Y	N	N
		Technical regulatory	Y	Y	Y	N	Y	Y	Y
		Other	N	N	N	N	N	N	N

18	**Which countries do you recognize or use regulatory decisions, reports, guidance or information from**	**Within SADC**	Zimbabwe, Tanzania, South Africa	None	None	None	None	Zimbabwe, Botswana and Namibia	ZAZIBONA participating countries
		Outside of SADC	Whole ICH Region	EU, CANADA, TGA, FDA	PIC/s countries	Inspection reports from PIC/S member countries	ICH Countries	-	ICH countries
19	**Have you registered products based on registration in other countries**	**Within SADC**	N	N	-	N	N	Y	N
		Outside of SADC	N	N	-	No specific data available as inspections is just one of the regulatory requirements to register a medicine.	Y - ICH Countries and WHO through Collaborative registration arrangements	-	Y - registrations in ICH countries; WHO PQ
20	**What are your perceptions or experiences of the Zazibona initiative**		It is a great initiative within the SADC Region to speed up market authorization and it's a great learning forum for the observers as well. All SADC member states should take part in this initiative,	A very good initiative by the four countries and need to be supported by SADC and a good model that should be inclusive of all SADC member states	I have not had any personal exposure to or interaction with the Zazibona inititative	Support the initiative	I personally participated in one session (March 2015). Assessment sessions are conducted by using stringent regulatory requirements. Sessions provides opportunity for capacity building of regulators from countries with limited regulatory capacity.-ZaZiBoNa assessments provides starting point for joint assessment and inspection activities in the SADC region	It has served as good way of sharing work, trust building and capacity building.	Zimbabwe is one of the founding countries and participate fully
21	**How do you think your country could benefit from the initiative**		It's a learning initiative and it would help in recognising the work done by this group and not have to redo the work in country once we start registration of medicines	Sharing of expertise and scarce skills within the region. Short turn-around times in product registration and inspections	N/A	Information sharing	The initiative could provide the following opportunities to my country: Receipt and sharing of regulatory information, Work sharing with other regulators and hence helps in reducing workload, Capacity building for regulatory officers, Availability of good quality medicines in the regional market and hence reduce prevalence of substandard medicines	Continued capacity building and work sharing. It would also lead to recognition of work by other countries including report sharing and decisions	Easier to share information and to collaborate
22	**What do you perceive as the major barriers to harmonization in the SADC region**		• Differences in the Legal frameworks • Differences in the application format (CTDs) • Issues of sovereignty	• Legislation differences • Differing Assessment standards • Perceived levels of expertise • Registration processes • National pride	• Trust building amongst regulatory authorities • Differences in or absence of national regulatory authorities	The different levels of Regulatory Development and maturity of the various National Medicines Regulatory Authorities within SADC.	• Dependency on external technical and financial support in regional activities • Lack of clear understanding of harmonization and benefits of harmonization in Partner States • Some countries in the region do not have well established medicines regulatory systems • Language barriers in few countries (e.g Mozambique, Angola and DRC)	• Use of different guidance documents • Difference in capacity levels of NMRAs • Funding for joint work	• Levels of development and systems among SADC countries • Capacity limitations in the SADC Member States to implement agreed positions / decisions

23	**What strategies are needed to improve regulatory harmonization in the SADC Region**	• Harmonization of Regulatory Framework • Harmonization of Application Format (CTDs/eCTDs) • Work-sharing such as ZAZIBONA	• Concentrate on scientific/ technical matter in terms assessment of product applications and inspections • And let individual regulatory authorities deal with legislative frameworks and registration processes	Formal systems need to be implemented and controlled	• Strategies are developed by each Regulator based on in country maturity. • No strategies developed by any outsider could be implemented by any NRA in SADC if the necessary resources, skills, expertise and political will are not present.	• Facilitate/Support establishment of National Medicines Regulatory bodies in the countries lacking such agencies • Establish links and strengthen political support in countries on SADC matters and specifically medicines regulatory harmonization • Establishment and strengthen joint assessments and inspections as pilot projects towards the overall regional harmonization • Building of capacity at the Secretariat to facilitate harmonization initiatives	• Adoption of regional guidelines by all countries • Establishment of training centers and modules of NMRA technical staff • Establishment of platform for secure information sharing • Identification of lead experts in thematic areas within the region.	moving with subset of countries that have similar systems • Build human recourse capacity within Member States

Appendix 4 – Ethics Approval

R14/49 Ms Amanda Calder

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150230

NAME: (Principal Investigator) Ms Amanda Calder

DEPARTMENT: Pharmacy and Pharmacology

PROJECT TITLE: Assessment of Potential Barriers to Medicines Regulatory Harmonization in the SADC Region

DATE CONSIDERED: 27/02/2015

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Shabir Banoo and Shirona Naidoo

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

DATE OF APPROVAL: 20/04/2015

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 25.04.2015

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 5 – 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, Amanda Calder (Student number: 875651) am a student registered for the degree of Master of Science in Medicine (Pharmaceutical Affairs) in the academic year 2016

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.

Signature:  Date: 28 April 2016