Perceptions of the Pharmaceutical Industry and Regulators in South Africa towards Registration Harmonisation in the Southern African Development Community (SADC)

KESHNEE DHANRAJ

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MARCH 2021

PROFESSOR ADMIRE DUBE

PROFESSOR KIM WARD

Declaration

I declare that this thesis that I now submit for assessment on the programme of study leading to the degree Master of Science in Pharmacy Administration and Policy Regulation has not been submitted for the purpose of a degree at this or any other higher education institution. It is entirely my own work and has not been taken from the work of others save to the extent that such work has been cited and acknowledged within the text of this work.

I agree to deposit this thesis in the University of the Western Cape's Library and Healthcare-Learning's institutional repository or allow these institutions to do so on my behalf, subject to South African and British copyright legislation and the University of the Western Cape's conditions of use and acknowledgement.

Signed…… Date: 7 March 2021

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Abstract

Medicines have to be regulated in an effort to monitor their quality, safety, and efficacy. The process of medicines registration is lengthy, costly, and document-heavy. Many countries have limited expertise and resources at national medicines regulatory authorities (NMRAs) and some countries have adopted unified approaches to medicines registration legislation. Harmonised guidelines and initiatives have been adopted in South Africa and the Southern African Development Community (SADC). However, there are no studies that have identified the effects of these initiatives and guidelines on major stakeholders such as the pharmaceutical industry and regulators. This study aimed to bridge that gap by exploring the views on the effects of harmonisation initiatives held by the pharmaceutical industry and national medicines regulatory authority (NMRA) regulators in South Africa.

This study uncovered the perceptions of forty-nine pharmaceutical industry professionals, mainly regulatory affairs professionals (RAPs), in South Africa with regards to whether harmonisation initiatives increase efficiency in their work environment, speed up registration approvals, benefit major stakeholders, and increase access to essential medicines. Other study objectives were to ascertain the RAPs' level of satisfaction with the pace at which harmonisation is progressing in SADC, at which new medicines are being registered in SADC, and at which these medicines are reaching the market in SADC. The study also elicited the RAPs' views on the perceived advantages and disadvantages of and barriers to harmonisation.

This study entailed a cross-sectional study design which utilised mixed research methods to analyse data. The survey consisted of Likert-type rating scales and open-ended questions. The survey was divided into two parts to extract respondents' perceptions of South African and SADC harmonisation initiatives separately.

There is definite agreement among pharmaceutical industry professionals that the harmonisation initiatives that have been adopted in South Africa and SADC help to increase efficiency in their workplace. They believe that the increase in efficiency has also positively affected NMRAs, speeding up approval timelines for essential medicines and generics, thereby increasing consumers' access to these medicines. It can be concluded that the study sample perceive that the positive effects of harmonisation may extend to all major stakeholders as a result of increased efficiencies.

There is no definite agreement among pharmaceutical industry professionals that harmonisation will speed up registration timelines for new chemical entities (NCEs). They believe that harmonisation is unlikely to affect registration timelines for NCEs. The pharmaceutical industry in South Africa is not satisfied with the pace at which harmonisation is progressing in SADC or the rate at which new medicines are reaching the market in SADC. This is further evidenced by the pharmaceutical industry professionals' rating that the pace at which new medicines are registered in SADC is slow to average.

There is a perception that harmonisation is unlikely to affect registration timelines for NCEs. The general perceptions are that harmonisation has had a positive effect on efficiency in the workplace, hence greater benefits to major stakeholders however the pharmaceutical industry were not satisfied with the progress of harmonisation initiatives, rate at which new medicines were registered and approval timelines in the SADC. This study also brought to light many advantages, disadvantages and barriers to harmonisation which may ultimately affect the pace at which harmonisation is progressing at in the SADC.

Keywords

Perceptions of medicines registration; medicines registration harmonisation in SADC; regulatory affairs; regulators; pharmaceutical industry; advantages of harmonisation; disadvantages of harmonisation; barriers to harmonisation

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List of Abbreviations

ADRs	adverse drug reactions
AMRHI	African Medicines Regulatory Harmonisation Initiative
APEC	Asia-Pacific Economic Cooperation
ASEAN	Association of Southeast Asian Nations
AU	African Union
CTD	common technical document
DOH	South African Department of Health
DRC	Democratic Republic of Congo
EAC	East African Community
ECOWAS	Economic Community of West African States
EU	European Union
FDA	US Food & Drug Administration
GBMSA	Generic and Biosimilar Medicines of Southern Africa
GMP	Good manufacturing practice
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IPASA	Innovative Pharmaceutical Association of South Africa
MCC	Medicines Control Council
NCEs	new chemical entities
NMRA	national medicines regulatory authority
PANDRH	Pan American Network for Drug Regulatory Harmonisation
RAPs	Regulatory affairs professionals
RRA	Recognised regulatory authority
SAAPI	South African Association of Pharmacists in Industry

SADC	Southern African Development Community
SAHPRA	South African Health Products Regulatory Authority
SAPRAA	Southern African Pharmaceutical Regulatory Affairs Association
SMASA	Self-medication Manufacturers Association of South Africa
SmPC	Summary of Product Characteristics
UK	United Kingdom
US	United States of America
WHO	World Health Organization
WHO CRP	WHO Collaborative Registration Procedure
WHO PQP	WHO Prequalification of Medicines Programme

CHAPTER 1
INTRODUCTION

1.1 BACKGROUND

The pharmaceutical market in Africa has been growing at a rapid pace. It is rated as the second fastest growing pharmaceutical market in the world (Juhi, Dedania, Dedania, Jain & Meghna, 2018). It is estimated to grow between US$8 and 10 billion a year (Juhi *et al*., 2018). Although the pharmaceutical market is growing rapidly, the African population is still plagued by several communicable and non-communicable diseases – to such an extent that the local pharmaceutical market is unable to keep up with the high demand for medicines (Juhi *et al*., 2018).

Even though there is a high demand for medicines on the continent, these products have to be adequately regulated to ensure that they are of good quality and are safe and efficacious before the public can access them. The national medicines regulatory authority (NMRA) in any given market is responsible for assessing the quality, safety, and efficacy of a medicine based on the chemistry, manufacturing and controls, and pre-clinical and clinical information provided during the registration process (Juhi *et al*., 2018). The major factors that have contributed to delays in medicines registration in Africa are lack of expertise at NMRAs, little to no harmonisation of regulatory standards amongst countries, resource constraints, and failure to rely on regulatory assessments conducted by other regulators or the World Health Organization (WHO) (Ndomondo-Sigonda, Miot, Naidoo, Ambali, Dodoo & Mkandawire, 2018). The complexity of medicines registration requirements amongst different African countries has prevented numerous pharmaceutical companies from pursuing registration of medicines in these markets (Luthuli & Robles, 2017).

NMRAs and the pharmaceutical industry have become more aware of the factors that hamper medicines registration. This is one of the reasons that a growing number of countries are moving towards harmonisation of existing medicines regulations, standards, and guidelines.

The first medicines harmonisation attempt was led by the European Union (EU) in the 1980s (Luthuli & Robles, 2017). This was a successful attempt at designing and implementing the framework for harmonisation in Europe. This is a model that the African Medicines Regulatory Harmonisation Initiative (AMRHI) intends to mimic (Luthuli & Robles, 2017). The AMRHI aims to harmonise technical requirements for medicines registration by conducting joint dossier reviews, sharing expertise for reviews, conducting joint good manufacturing practice (GMP) inspections, and streamlining the decision-making processes (Ndomondo-Sigonda *et al.*, 2018). This initiative has contributed positively to improving medicines registration approval timelines in Africa (Ndomondo-Sigonda *et al.*, 2018).

1.2 RATIONALE

Medicines that are not regulated effectively have shown to have deleterious consequences for consumers. It is therefore important that every country has medicines regulations, as well as an effective NMRA to enforce regulations. The new NMRA in South Africa, known as the South African Health Products Regulatory Authority (SAHPRA), has adopted numerous new guidelines that aim to promote harmonisation. As of July 2019, SAHPRA had implemented harmonised guidelines for certain regulatory activities. These harmonised guidelines are new for both the South African pharmaceutical industry and regulators. SAHPRA is also an active member of the ZaZiBoNa collaborative initiative for harmonisation in the Southern African Development Community (SADC). It is therefore important to understand how the pharmaceutical industry and regulators in South Africa perceive South African and SADC harmonisation initiatives. This provides insight into how cooperative stakeholders will be

toward these initiatives. The SADC was chosen as a focus market for this study as it has made significant progress towards regulatory harmonisation.

There are a number of studies on harmonisation initiatives and how these have progressed to date within Africa (Azatyan, 2013; Luthuli & Robles, 2017; Ndomondo-Sigonda *et al*., 2018). Numerous researchers have also assessed the advantages and disadvantages of harmonisation initiatives (Calder, 2016; Singh, 2015; Sithole, Mahlangu, Salek & Walker, 2020; WHO, 2013 & 2014a). However, there is a lack of academic investigation into the impact of harmonisation initiatives on major stakeholders such as NMRAs and the pharmaceutical industry.

Regulators at the NMRAs and the pharmaceutical industry in SADC have become accustomed to working according to their respective laws, regulations, standards, and guidelines. Although research has shown that harmonisation greatly reduces the workload for regulatory affairs professionals (RAPs) in the pharmaceutical industry and NMRAs (Valverde, 2015), there could be resistance to change, especially in South Africa as a result of the new guidelines and ways of working. Resistance may come from more experienced RAPs that have become accustomed to old ways of working. This means that all RAPs will have to be retrained on the new guidelines thereby making it more time consuming to complete regulatory documentation. The regulatory affairs industry may now have to spend more resources on training RAPs than before.

It is therefore important to identify the perceptions and attitudes of major stakeholders, such as NMRAs and the pharmaceutical industry, of the impact that harmonisation initiatives will have on them. Harmonisation initiatives will prove to be futile if they are not fully supported by major stakeholders. Perceptions are important to investigate as these factors can determine how cooperative industry and regulators can be with regard to harmonisation initiatives. Greater cooperation will result in successful implementation of these initiatives.

1.3 STUDY AIMS AND OBJECTIVES

The aim of the study is to gauge the perceptions of the pharmaceutical industry and NMRAs in South Africa toward medicines registration harmonisation initiatives in South Africa and in SADC.

The objectives of this study were to:

- determine perceptions on whether harmonisation initiatives have led to increased efficiency in the work environment and improved registration approvals
- determine perceptions on whether harmonisation initiatives benefited major stakeholders such as the consumer, regulators and the pharmaceutical industry
- determine perceptions on the pace at which new medicines are being registered in SADC and rate at which these medicines are reaching the market
- determine perceptions on the pace at which harmonisation is progressing in SADC
- determine stakeholder's perceived advantages, disadvantages and barriers to harmonisation initiatives

1.4 ETHICS APPROVAL

This study was approved by the Humanities and Social Science Research Ethics Committee (HSSREC) of the University of the Western Cape in April 2020. The approval letter from the HSSREC is attached as Appendix B.

CHAPTER 2
LITERATURE REVIEW

2.1 INTRODUCTION

This study was centred around the perceptions of the pharmaceutical industry and regulators in South Africa regarding medicines registration harmonisation initiatives in Africa. The study was focused specifically on SADC countries. The reason for the focus on SADC was because of the new guidelines that SAHPRA have adopted and the various successes that the SADC ZaZiBoNa harmonisation initiative had achieved thus far. The research questionnaire and some parts of the thesis referred to the ZaZiBoNa collaborative initiative as a harmonisation initiative however it is also a collaborative regional joint activity that involves work sharing. For the purposes of this research project the harmonisation part of ZaZiBoNa collaborative initiative was highlighted.

This literature review begins with a brief history of medicines regulation and an overview of NMRAs and their functions. The review then looks at the new SAHPRA organisation and the initiatives it has adopted to align with global NMRAs. The next section addresses harmonisation, details of regional and African harmonisation initiatives, and the barriers to, disadvantages and benefits of harmonisation. The review ends with a conclusion, key findings, and gaps in the current literature that this study intends to fulfil.

2.2 THE HISTORY BEHIND MEDICINES REGULATION

The process of medicines registration and regulation is a complex and lengthy one. However, history has shown that this process is necessary to ensure that only good quality, safe, and effective medicines circulate in a given market. The sulfanilamide and thalidomide tragedies of 1937 and 1961 respectively are examples of cases in which medicines have caused death

and severe adverse drug reactions (ADRs) (Ballentine, 1981; Rehman, Arfons & Lazarus, 2011). This was the turning point for medicines regulation and led to the development of stricter controls around the quality, safety, and efficacy of drugs circulating in the United States of America (US) in 1938 and the United Kingdom (UK) in 1963 (Ballentine, 1981; Rago & Santoso, 2008). A few case studies relating to the history and evolution of medicines regulations are presented below.

2.2.1 The Sulfanilamide Elixir Saga

Sulfanilamide in powder and tablet form was extensively used in the treatment of streptococcal infections and were shown to be safe for consumption (Ballentine, 1981). There was a demand for the drug to be available as a liquid. Therefore, it was dissolved in diethylene glycol and tested for organoleptic properties only; the formulation was not tested for toxicity and it was shipped throughout the US (Ballentine, 1981). At this time, the US Food & Drug Administration (FDA) did not require new drugs to undergo any safety testing. The sulfanilamide elixir was responsible for the death of more than one hundred people between September and October 1937 (Ballentine, 1981). The American Medical Association later discovered that diethylene glycol was the toxic excipient in the elixir that caused the many deaths (Ballentine, 1981). The 1938 Food, Drug, and Cosmetic Act was passed in the US as a result of the deaths caused by the sulfanilamide elixir (Ballentine, 1981). This Act stipulated that all new drugs had to have a pre-market notification (Rago & Santoso, 2008).

2.2.2 The Thalidomide Tragedy

Thalidomide was first sold as a sedative drug. However, it later became more widely used as an anti-emetic for many women around the world for the treatment of morning sickness

(Rehman *et al.*, 2011). The popularity of this drug was as a result of it being easily accessible over the counter to the public and its affordability (Rehman *et al.*, 2011). In the late 1950s thalidomide was marketed in forty-six countries (Tantibanchachai, 2014). However, in 1961, independent investigational studies showed that thalidomide was linked to congenital malformations in pregnancies (Rehman *et al*., 2011). This drug was responsible for more than ten thousand birth defects globally (Tantibanchachai, 2014). In 1963, a Committee on the Safety of Drugs was established in the UK, followed by the Yellow Card Scheme, a voluntary ADR reporting system, in 1964 **(**Rago & Santoso, 2008). The thalidomide tragedy resulted in the American Congress passing the 1962 Kefauver-Harris Amendments to the 1938 Food, Drug, and Cosmetic Act which would later be called the 1962 Amendments (Tantibanchachai, 2014). These amendments stipulated that any drug manufacturer must prove both safety and efficacy of a product prior to it being sold on the market (Tantibanchachai, 2014). Prior to the amendments, the Food, Drug, and Cosmetic Act only required a new drug to be safe. The Drug Amendment Act of 1962 required the FDA to approve all new drug applications, thereby assessing the drug's safety and efficacy in order to avoid another disaster such as that caused by thalidomide (Rago & Santoso, 2008).

It was unfortunate that even after the sulfanilamide saga not all countries deemed it important to adopt medicines regulations to ensure the safety of drugs for consumers. It was only after the thalidomide tragedy that the UK put in place measures to monitor the safety of drugs. The thalidomide and sulfanilamide tragedies were turning points in history for medicines regulation. These incidences highlighted the importance of countries having effective medicines regulations to ensure quality, safety, and efficacy of products. Every country also needs an effective NMRA to help enforce these regulations.

2.3 FUNCTIONS OF NMRAs

All countries should have an effective NMRA to ensure that legislation is enforced and products are adequately regulated. NMRAs in each country have the responsibility to ensure that medicinal products circulating in their respective markets are safe, efficacious, and of high quality (WHO, 2008). NMRAs were first formed in the UK (1880s), Switzerland (1900), the US (1906), Norway (1928), and Sweden (1934) with the aim of safeguarding patents and dealing with trade promotions (Ndomondo-Sigonda, Miot, Naidoo, Dodoo & Kaale, 2017).

The main functions of NMRAs are licensing medicines in terms of manufacture, import, export, distribution, promotion, and advertising and issuing marketing authorisation after the safety, efficacy, and quality of the medicines have been assessed (WHO, 2003). They are also responsible for carrying out the necessary inspections for manufacturers, importers, wholesalers, and dispensers of medicines (WHO, 2003). Their other functions include monitoring and controlling the quality of medicines on the market, monitoring ADRs of medicines, and providing unbiased information on medicines to healthcare professionals and consumers (WHO, 2003). NMRAs may also take on other tasks such as overseeing clinical trials (Hill & Johnson, 2004).

The capacity of NMRAs varies amongst countries (WHO, 2020a). Some NMRAs are found within governmental departments of health, whereas others function almost independently (Ndomondo-Sigonda *et al*., 2017). Some NMRAs regulate food and medicine under the same regulations, such as the US FDA (Hill & Johnson, 2004) and the National Agency for Food and Drug Administration and Control in Nigeria. Other markets regulate products such as cosmetics, household chemicals, health supplements, disinfectants, medical devices, complementary medicines, veterinary medicines, and agricultural chemicals (Hill & Johnson, 2004).

The WHO has highlighted the main factors that contribute to an effective NMRA as described in Table 2.1 below.

Table 2.1: Factors that contribute to an effective NMRA

General Factors	Factors within the NMRA
• Support with regards to political will and a strong commitment to regulations • Adequate supply of medicines at reasonable prices • Public support for medicines regulation • Sound and effective communication and collaboration between the NMRA and law enforcement agencies such as the police or customs • Adequate number of trained and skilled professionals • Control of export and e-commerce of medicines • Political environment that favours independent decision-making	• Clear mission and vision • Clear and adequate legislation and regulation • Appropriate organisation structure and infrastructure • Clearly defined roles and responsibilities within the organisation • Adequate financial resources to upskill and retain human resources • Appropriate standards, guidelines, and procedures in place • Effective collaboration and communication between NMRAs and stakeholders • Accountability and transparency • Effective and appropriate management systems

Source: WHO (2003)

NMRAs need to operate in environments with enough political support and adequate financial resources with the adequate legislative frameworks in place (Hill & Johnson, 2004). Human resources are a major issue at NMRAs in developing countries with the main concerns being a lack of skilled individuals for inspections and dossier assessments, low salaries, poor working conditions, and a lack of career development opportunities (Ndomondo-Sigonda *et al*., 2017). The former NMRA in South Africa, known as the Medicines Control Council (MCC), was one such NMRA that was faced with resource constraints, poor service delivery, limited scope for harmonisation initiatives, a paper-based document management system, and a lack of transparency and accountability with respect to stakeholder relationships (Keyter, Gouws, Salek, & Walker 2018b). This caused the MCC to be ineffective and hence there was a need

for change within the organisation. The study by Keyter *et al*. 2018b was designed to assess the regulatory process in South Africa from 2015 to 2017, identify timelines and milestones in the review process, evaluate measures to ensure transparency and predictability and review the challenges and opportunities for enhanced regulatory practices in South Africa hence the statement regarding the inefficiencies at the MCC was based on the author's opinion and not on the actual findings of the study.

2.4 THE ESTABLISHMENT OF SAHPRA

The Drugs Control Act (Act 101 of 1965) is now known as the Medicines and Related Substances Act (Act 101 of 1965) and has been amended numerous times. The latest amendments include the establishment of SAHPRA.

The newly amended Act has mandated for the establishment of SAHPRA, which is a separate juristic person outside of the National Department of Health and which replaces the former NMRA, the MCC (Keyter, Banoo, Salek & Walker 2018a). The legislative mandate of SAHPRA originates from the Constitution, National Health Act (Act 61 of 2003), the Medicines and Related Substances Act (Act 101 of 1965, as amended) and the Hazardous Substances Act (Act 15 of 1973) (SAHPRA, 2020b). The SAHPRA was established in February 2018 (Keyter *et al.*, 2018a). As per the Medicines and Related Substances Act (Act 101 of 1965), SAHPRA is authorised to regulate health products in the country by monitoring, evaluating, investigating, inspecting, and registering all health products in South Africa (SAHPRA, 2020a).

2.4.1 SAHPRA's Harmonised Guidelines

The SAHPRA have harmonised certain policies and procedures with the European Medicines Agency (EMA) which are aligned to ICH (SAHPRA, 2019a). SAHPRA have adopted EMA guidelines for quality and bioequivalence requirements to reflect global best practices for

health product regulation (SAHPRA, 2019a). The latest package insert format has been adopted from the EMA summary of product characteristics (SmPC) with a few additions for local requirements (SAHPRA, 2019b). The SAHPRA have also adopted new review pathways as detailed in section 2.4.2.

2.4.2 SAHPRA's Review Pathways

SAHPRA have adopted four review pathways for the evaluation of new product applications and variations (SAHPRA, 2019a). Product dossiers will be reviewed through a full review, abridged review, or verified review process, or recognition pathway (Keyter *et al.*, 2018b). Table 2.2 provides more detail on the review pathways implemented at SAHPRA.

Table 2.2: SAHPRA's Review Pathways

Type of Review	When will this Type of Review be utilised
Full Review	• Variation or new product application that has not been registered or approved by a recognised regulatory authority (RRA) • Lack of reliance documents
Abridged Review	• New medicine application for a generic that is registered by an RRA • New registration for a WHO prequalified product • Type II variation that has been approved by an RRA • Backlog specific for new registrations of generics or new chemical entities (NCEs) that have received prior pharmaceutical and analytical committee approval and information relevant to the approval has been updated
Verified Review	• New registration application for an NCE registered by an RRA • Type IB variation that has been approved by an RRA • Backlog specific for new registrations of generics or NCEs that have received prior pharmaceutical and analytical committee approval and information relevant to the approval has not been updated
Recognition	• SAHPRA is in the process of negotiating recognition agreements with RRAs • Applications may not need to be evaluated by SAHPRA if they are approved by RRAs that SAHPRA has a recognition agreement with • A framework will be published for the implementation of this type of review

Source: SAHPRA (2019)

Literature is scarce on the SAHPRA's review pathways and harmonised guidelines hence actual SAHPRA published guidelines were used as references. The SAHPRA publication mentions scope for recognition-based review and publication of a framework for the implementation of this type of review however no timelines have been established for this. The recognition pathway, verified review, and abridged review are intended to result in faster approvals by SAHPRA. This form of work-sharing and collaboration may have a positive impact on all stakeholders. The new legislation related to SAHPRA and the guidelines have been developed to address the changing needs of the South African public and aligns South Africa with international RRAs (Department of Health [DOH], 2018).

2.4.3 SAHPRA's Recognised Regulatory Authorities (RRAs)

The WHO have encouraged NMRAs to prevent duplication of efforts through collaboration and recognition of work done at other NMRAs to reduce the regulatory burden (WHO, 2014a). As mentioned previously, verified and abridged reviews and the recognition pathway are types of reliance-based evaluations in which SAHPRA will utilise assessment reports from RRAs. The NMRAs in Europe (namely, the European Medicines Agency), Canada, the UK, Japan, Switzerland, Australia and the US are regarded as RRAs (SAHPRA, 2019a). SAHPRA not only recognises work done by other more developed and resourced NMRAs but may also utilise the WHO Prequalification of Medicines Programme (PQP) and the ZaZiBoNa procedure assessments for a reliance-based review (SAHPRA, 2019a). The WHO PQP is discussed in more detail in Section 2.5.

2.5 WHO PQP

The WHO Collaborative Registration Procedure (CRP) received approval from the World Health Assembly in 2013 (WHO, 2013). Dossier evaluations are conducted by experts from developed and developing countries (Moran, Strub-Wourgaft, Guzman, Boulet, Wu & Pecoul, 2011). Dossiers for prequalification are submitted in the common technical document (CTD) format (WHO, 2013). The WHO PQP prequalifies in-vitro diagnostics, certain vaccines, some immunisation devices, vector control products, and medicines (WHO, 2020b). The medicines that are prequalified include treatments for human immunodeficiency virus (HIV), malaria, tuberculosis, reproductive health, hepatitis, diarrhoeal diseases, and certain tropical diseases (WHO, 2020b). The WHO CRP was developed in an effort to help NMRAs by relying on work already done by the WHO PQP (Goñi, 2016). New NMRAs participating in the WHO CRP may bring new innovative ideas and experiences to this way of working (WHO, 2013). The WHO CRP shares confidential and specific information from the WHO PQP with the relevant NMRA in an effort to accelerate regulatory approval (Goñi, 2016). The WHO PQP also provides post-marketing surveillance of medicines (Doua & Van Geertruyden, 2014). Even though WHO prequalified medicines are tested against international standards, these medicines still need to be approved by NMRAs in individual countries (WHO, 2013). The WHO CRP also assists NMRAs in building their own capacities by leveraging the work done by the WHO PQP (WHO, 2013). The WHO CRP contributes to speeding up the registration of WHO-prequalified medicines as a result of increased collaboration between the WHO PQP and NMRAs (WHO, 2013). This is what SAHPRA intends to leverage for reliance-based reviews. SAHPRA has adopted these reliance-based approaches for reviews in an effort to speed up approvals and decrease the workload at the NMRA. It has adopted and implemented certain new policies and procedures in an effort to align with the European Medicines Agency (SAHPRA, 2020b). These new changes within the NMRA can be quite overwhelming to RAPs

in the pharmaceutical industry and NMRAs, hence there is a need to understand how these stakeholders perceive these changes that have been made. This study aims to understand the perceived impact of these changes on major stakeholders such as RAPs in the pharmaceutical industry and NMRAs. This study will focus on SADC as this region have made significant progress with initiatives to accelerate medicines registrations in the region.

2.6 OVERVIEW OF SADC

SADC was first formed in 1980 as an alliance of nine Southern African countries and was formerly known as the Southern African Development Coordination Conference, there was a transformation from a Coordinating Conference into a Development Community in 1992 (SADC, 2012). The SADC have brought sixteen countries together to enhance economic growth, counteract poverty, support the disadvantaged through regional integration, and enhance the quality of life of the Southern African people (SADC, 2012). SADC member states are Angola, Botswana, Comoros, Democratic Republic of Congo (DRC), Eswatini, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Tanzania, Zambia, and Zimbabwe (SADC, 2012). The SADC has no single regional NMRA for all member states. Each member state has its own NMRA and some member states have no NMRAs. The names and responsibilities of SADC NMRAs are detailed in Table 2.3.

Table 2.3: NMRAs in SADC and their Responsibilities

Country	Name of NMRA	Responsibility
South Africa	SAHPRA	Regulating health products intended for human and animal use Licensing manufacturers, wholesalers, and distributors of medicines, medical devices, radiation emitting devices, and radioactive nuclides Conducting clinical trials (SAHPRA, 2020c)

Zimbabwe	Medicines Control Authority of Zimbabwe (MCAZ)	Protecting public and animal health by ensuring that medicines, allied substances, and medical devices are safe, effective, and of good quality through enforcement of adherence to standards by manufacturers and distributors (MCAZ, 2019)
DRC	Directorate of Pharmacy and Medicine (Direction de la Pharmacie et du Médicament)	Allowing clinical trials and authorising and controlling drug imports and exports (National Institute of Allergy and Infectious Diseases, 2020a)
Zambia	Zambia Medicines Regulatory Authority (ZAMRA)	Regulating and controlling the manufacture, importation, storage distribution, supply, sale, and use of medicines and allied substances (ZAMRA, 2020)
Malawi	Pharmacy and Medicines Regulatory Authority (National Institute of Allergy and Infectious Diseases, 2020b)	Regulating medicines and pharmacy practice and enforcing associated legal provisions in the country's legislation (Public Service Reforms, 2020)
Madagascar	L'Agence du Médicament de Madagascar	Registering drugs and other health products as defined in the Health Code in order to grant them a Certificate for Marketing in Madagascar (WHO, 2016a)
Seychelles	Medicines Regulatory Authority*	Inspecting, import control, licensing, market control, and quality control (Seychelles Ministry of Health, 2011)
Namibia	Namibia Medicines Regulatory Council (NMRC)	Reviewing application dossiers submitted for the registration of medicines, related substances, and medical devices Reviews of all post-registration amendments made to any registered medicines, related substances, and medical devices Licensing and registering premises (NMRC, 2015)
Tanzania	Tanzania Medicines and Medical Devices Authority	Inspecting, enforcing, testing, analysing, evaluating, and registering medicines, medical devices, and diagnostics Importing, exporting, distributing, and manufacturing medicines, medical devices, and diagnostics Controlling clinical trials and pharmacovigilance (National Institute of Allergy and Infectious Diseases, 2019)
Botswana	Botswana Medicines Regulatory Authority (BOMRA)	Regulating medicines, medical devices, and cosmetics to promote human and animal health (BOMRA, 2020)
Mozambique	Direcção Nacional de Farmácia (DNF)	Regulating and controlling medical products, such as medicines, vaccines, and other biological and health products for human use, within the highest quality standards (DNF, 2018)
Mauritius	Ministry of Health & Quality of Life	Registering medicines and other products, inspecting, import control, licensing, market control, quality control, medicines advertising and promotion, and pharmacovigilance (Ministry of Health and Quality of Life of Mauritius, 2011)

Eswatini	Ministry of Health	Providing preventive, promotive, curative, and rehabilitative services that are of high quality, relevant, accessible, affordable, equitable, and socially acceptable to improve the health status of citizens (Swaziland Ministry of Health, 2020)
Angola	Ministry of Health National Directorate for Pharmaceuticals and Equipment (DNME)	Monitoring the quality of imported pharmaceuticals and medical equipment Ensuring that medical devices imported into the country meet WHO norms and Angolan regulations Establishing the criteria for pharmaceuticals and medical equipment entry into Angola (Export.gov, 2018)
Comoros	Direction des Etablissements de soins Publics et privés	Responsible for implementing and enforcing regulations (WHO, 2014b)

*The Medicines Regulatory Authority of Seychelles is not responsible for medicines registrations, medicines advertising and promotion, clinical trials controls and pharmacovigilance.

There are fifteen member states have NMRAs. However, the responsibilities of each NMRA differs. Most of the NMRAs assess products for quality, safety, and efficacy, whereas other NMRAs just control imports. Lesotho has no NMRA (WHO, 2012). The variation in responsibilities amongst the different NMRAs has made it difficult to align medicines regulations. However, the SADC have managed to successfully implement harmonisation initiatives. The next section will provide more background for the concept of harmonisation as well as insight into global and African harmonisation initiatives that have been adopted.

2.7 INSIGHT INTO AND HISTORY OF REGULATORY HARMONISATION

Variations with respect to technical requirements from country to country have made it necessary to duplicate expensive testing in order to obtain medicines registration approval (Singh, 2015). This called for an urgent need to harmonise and rationalise regulations as a result of exorbitant healthcare costs, increased cost of research and development, and the need to meet consumer expectations for faster speed to market of innovative, safe, and effective new medicines (International Council for Harmonisation [ICH], 2020.).

Regulatory harmonisation is a process whereby NMRAs agree on and align to acceptable technical requirements needed for the development and marketing of pharmaceutical products (FDA, 2020). The harmonisation of regulatory requirements was introduced in the 1980s by the European Community (ICH, 2020). The European Community initiated the harmonisation of regulatory requirements as a trade-driven initiative with the purpose of developing a body for pharmaceutical regulations and legislation in member states (Reggi, 2017).

2.7.1 Background on the International Conference on Harmonisation

RAPs from Europe, Japan and the US came together for the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (WHO, 2016b). The resultant council is now known as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and consists of more members and observers from around the world (ICH, 2020). The ICH was purely focused on the development of guidelines and standards for use by ICH member states in the first decade of the ICH being established. However, in 1999, the ICH established the Global Cooperation Group as a result of the growing interest in ICH guidelines and standards with other non-ICH states (Valverde, 2015).

2.7.2 ICH Objectives and Guidelines

The ICH's objective is to increase international harmonisation of technical requirements required to ensure that medicines are registered in the most efficient and cost-effective manner (Mahaparale & Desai, 2018). The ICH have published safety, efficacy, quality, and multidisciplinary guidelines for medicines regulation (ICH, 2020). Table 2.4 details the specific aspects that each guideline covers.

Table 2.4: Specific Aspects that each ICH Guideline covers

Guideline	Aspects Covered by the Guideline
Quality	Stability, analytical validation, pharmacopoeias, topics relevant to GMP and quality risk management, amongst other topics
Safety	Information on genotoxicity, reproductive toxicity, and other safety evaluations
Efficacy	Relates to the design, conduct, safety, and reporting of clinical trials
Multidisciplinary	Medical terminology, CTDs and the development of electronic standards for the transfer of regulatory information

Source: Singh (2015)

The ICH guidelines have helped in promoting harmonisation in many regions across the globe. The Asia-Pacific Economic Cooperation (APEC), Association of Southeast Asian Nations (ASEAN), East African Community (EAC), Gulf Cooperation Council, Pan American Network for Drug Regulatory Harmonisation (PANDRH) and SADC are all observers of the ICH (ICH, 2020).

2.8 REGIONAL HARMONISATION INITIATIVES

2.8.1 APEC

There are twenty-one member states that belong to APEC, namely the US, Australia, Brunei Darussalam, Canada, Chile, China, Hong Kong, Indonesia, Japan, Malaysia, Mexico, New Zealand, Papua New Guinea, Peru, the Philippines, Russia, Singapore, Republic of Korea, Chinese Taipei, Thailand, and Vietnam (Brennan, 2019). Each state is responsible for determining the level of convergence it requires and developing specific strategies to encourage regulatory convergence based on a timeline in the context of its own regulatory system and sociocultural objectives (APEC, 2020). Regulatory convergence is a voluntary process in which the regulatory requirements across states become more similar or even aligned over a period of time as a result of the slow phasing in of internationally recognised technical guidance

documents, standards and scientific principles, and common or similar practices and procedures (APEC Life Sciences Innovation Forum Regulatory Harmonization Steering Committee, 2020). The Regulatory Harmonisation Steering Committee was initiated in 2009 and is responsible for identifying key areas that members believe would benefit from regulatory convergence (APEC, 2020).

2.8.2 ASEAN

The member states of ASEAN include Brunei Darussalam, Cambodia, Indonesia, Lao People's Democratic Republic, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam (ASEAN, 2020). ASEAN NMRAs have successfully developed harmonised technical requirements for the registration of pharmaceuticals, as well as harmonised guidelines for the application and interpretation of the technical requirements (Reggi, 2017). Most of the regulatory guidelines have been harmonised with the ICH or the EU guidelines (Tongia, 2018).

2.8.3 Gulf Cooperation Council

There are seven Gulf Cooperation Council member states, namely Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, and Yemen (Sravani, Gowthami, Prabhahar & Rama Rao, 2017). The Gulf Central Committee for medicines registration was adopted in 1998 and is responsible for numerous activities, such as the registration of drugs and pharmaceutical companies according to harmonised registration regulations and GMP inspections (Gulf Health Council, 2020). The Committee has adopted the EU centralised and decentralised procedures for medicines registration (Sravani *et al*., 2017).

2.8.4 PANDRH

PANDRH was initiated in 1999 and supports regulatory harmonisation in the Americas (Pan American Health Organization, 2020). PANDRH's mission is to promote regulatory convergence for health products in all areas of quality, safety, efficacy, and rational use while strengthening NMRA capacities in the region of the Americas (FDA, 2019).

These are just some of the regional harmonisation initiatives that have been adopted globally. These harmonisation initiatives have been started before African harmonisation initiatives. However, in the last decade Africa has made significant progress towards harmonisation initiatives.

2.9 AFRICAN HARMONISATION INITIATIVES

2.9.1 The Development and Objectives of the AMRHI

The AMRHI was formalised in 2009 and launched in the EAC in 2012 (Luthuli & Robles, 2017). The objectives of the AMRHI include:

- fostering collaboration through partnerships,
- harmonising technical requirements for the regulation of medicines,
- conducting joint dossier evaluations and inspections,
- strengthening regulatory oversight and capacity,
- and developing effective information management systems to enhance the exchange of regulatory information (WHO, 2008).

This programme was developed through the joint partnerships between the New Partnership for Africa's Development (NEPAD), Pan African Parliament, African Union (AU) Commission, WHO, World Bank, Bill and Melinda Gates Foundation, and the UK's

Department for International Development (Luthuli & Robles, 2017). The AMRHI was funded by a trust fund established by various global partners (Goñi, 2016). The AMRHI have also initiated the Biennial Scientific Conferences on Medical Products Regulation in Africa (SCoMRA) for networking, collaborating, sharing best practices and lessons learned, and reflecting on work already accomplished (Ndomondo-Sigonda *et al.*, 2018).

The AU Model Law was developed by the AMRHI to promote harmonisation and ensure effective regulation (Ndomondo-Sigonda *et al.*, 2018). The AU Model Law for Medical Products Regulation has allowed for member states of the AU to adopt best practices from other medicines regulations into their national legislation (United Nations Development Programme, 2017). The ultimate goal of the AU Model Law is to resolve differences in medicines registration legislation, thereby improving efficiency and effectiveness of regulatory procedures across member states (Luthuli & Robles, 2017).

2.9.2 The Function of Regional Centres of Regulatory Excellence (RCOREs)

NEPAD and the AU Commission developed regional networks for the implementation of the AMRHI (Luthuli & Robles, 2017). There are eleven RCOREs operating across Africa in South Africa, Zimbabwe, Uganda, Burkina Faso, Ghana, Tanzania, Kenya, and Nigeria (NEPAD Agency & PATH, 2016). RCOREs have helped provide training in regulatory sciences applicable to various regulatory functions, facilitated upskilling of personnel through on-the-job training, twinning, and exchange of information, provided hands-on training through placements in the pharmaceutical industry, and have initiated for the development of best practices for scaling up to other NMRAs through testing interventions and innovations (NEPAD Agency & PATH, 2016). RCOREs play an important role in building regulatory capacity in Africa, thereby increasing the number of qualified and experienced individuals in

the pharmaceutical industry (NEPAD Agency & PATH, 2016). This will ultimately help to increase access to essential medicines and decrease the distribution of falsified, substandard, and counterfeit medicines in Africa through proper control over imports, exports, promotion, advertising, and distribution of medicines (NEPAD Agency & PATH, 2016). Essential medicines are those that satisfy the important health care needs of the population (WHO, 2021).

2.9.3 Regional Economic Communities (RECs) in Africa

There are five RECs that have started interacting with the AMRHI, as depicted in Figure 2.1 (NEPAD Agency, WHO, Bill & Melinda Gates Foundation, World Bank, Department for International Development & Clinton Health Access Initiative, 2010). The Economic Community of West African States (ECOWAS) committed to the AMRHI in February 2015 while SADC made progress toward AMRHI commitment in July 2015 (Goñi, 2016). The next sections give more insight into harmonisation activities in the EAC and SADC. These two RECs were chosen as they have made significant progress on harmonisation within their regions.

Figure 2.1: African RECs that have started interacting with the AMRHI

Source: NEPAD Agency et al. *(2010)*

2.9.4 Harmonisation in the EAC

The EAC was established in 1999 and consists of Kenya, Uganda, Rwanda, Burundi, and Tanzania (WHO, 2016b). Chapter 21, Article 118 of the EAC Treaty states that member states should harmonise medicines registration procedures in an effort to have good control of pharmaceutical standards without hampering the movement of pharmaceutical products, thereby increasing access of pharmaceuticals to consumers (WHO, 2016b). In 2012 the EAC was the first REC in Africa to begin with harmonisation efforts under the new AMRHI (Goñi, 2016) when the EAC's medicines regulation harmonisation effort was launched in Tanzania (WHO, 2014c). The main aim of this project was to ensure harmonisation across countries with regards to medicines regulations through collaboration and information-sharing (WHO, 2014c). The WHO supported this project with technical working groups, provided training, built capacities, and developed harmonised ways of working for the registration of medicines (Azatyan, 2013). Four working groups have been developed under this EAC project to deal with CTDs, GMP, and information-management and quality-management systems (WHO, 2014c). Marketing authorisation is issued via one of three processes, namely the National

Authorisation Procedures, WHO Collaborative Procedure, or the EAC Joint Assessment Procedure in which a joint review of the medicine applications together with a joint inspection of the manufacturing facility are conducted.

2.9.5 Harmonisation in SADC

The SADC Treaty makes provision for harmonisation of medicines regulations (Kamwanja, Saka, Awotedu, Fute, Chamdimba & Ndomondo-Sigonda, 2010). NMRAs from Zambia, Zimbabwe, Botswana, and Namibia took the initiative to collaborate on medicines registration with the support from the WHO PQP and the Southern African Regional Programme on Access to Medicines and Diagnostics (Goñi, 2016). This initiative is called ZaZiBoNa, and has been in operation for just over six years (Sithole *et al*., 2020). It was formed to address problems in NMRAs such as increased product applications, increased human resource turnover, lengthy approval timelines for registration of medicines, a lack of technical experience to assess certain applications, and a lack of financial resources (Sithole *et al*., 2020). Currently there are nine SADC member states that are active participants in ZaZiBoNa. Up to October 2019, 289 products had been assessed under ZaZiBoNa, either fully or partially, consisting of 274 generic applications, four new chemical entities (NCEs), and 11 biologicals or biosimilars (Sithole *et al*., 2020). The target median time for a response via ZaZiBoNa is nine months (Sithole *et al*., 2020). As at September 2019, 38 manufacturing-site GMP inspections and 19 desktop reviews had been conducted (Sithole *et al*., 2020). These numbers clearly highlight the effectiveness of this harmonisation initiative in SADC (Sithole *et al*., 2020). ZaZiBoNa's work is limited to the assessment of essential medicines. However, medicines that appear on the list of the United Nations (UN) Commission for Life-Saving Commodities for Women and Children may also be considered for review (Luthuli & Robles, 2017). The scope for ZaZiBoNa could be

expanded to include treatments for other diseases that are endemic to Africa (Sithole *et al*., 2020). The assessment of product dossiers takes place every quarter in a participating member state on a rotational basis (Sithole *et al*., 2020). A product must be submitted to at least two countries in the ZaZiBoNa group (Goñi, 2016). The applicant must mention that they are submitting a product for review under ZaZiBoNa (Sithole *et al*., 2020). Once the review process has begun, the group appoints a country known as the "rapporteur" to lead the assessment. The rapporteur then compiles a draft assessment report that is discussed with all NMRAs, and finalises the consolidated assessment report (Goñi, 2016). A country can only be an active participant in ZaZiBoNa if it has medicines registration legislation equivalent to SADC or WHO medicines registration guidelines and has the capacity to conduct GMP inspections (Sithole *et al*., 2020). SADC member states that do not meet these requirements will be observers in ZaZiBoNa and are not able to contribute to the assessment of product dossiers or participate in GMP inspections (Sithole *et al*., 2020). Angola, Seychelles, Eswatini, and Madagascar are currently observers of ZaZiBoNa (Sithole *et al*., 2020). Botswana, Namibia, Zambia, Zimbabwe, South Africa, the DRC, Mozambique, Malawi, and Tanzania are active participants in ZaZiBoNa, while Comoros, Lesotho, and Mauritius do not participate in ZaZiBoNa (Sithole *et al*., 2020). Figure 2.2 illustrates the active participants together with their initiation dates.

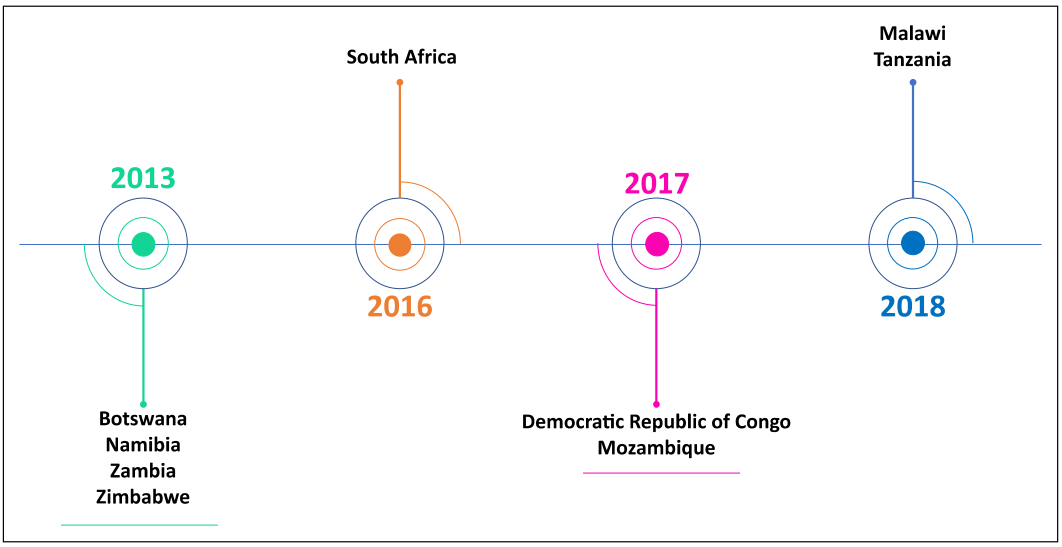

Figure 2.2: Active Participants of ZaZiBoNa and their Dates of Initiation

Source: Sithole et al. *(2020)*

Literature has revealed that the ZaZiBoNa collaborative initiative has been very successful in SADC to date (Sithole *et al*., 2020). Sithole *et al*., 2020 have reviewed numerous literature sources to provide a critical review of the ZaZiBoNa process and factors that have contributed to its success and those that negatively affect the process. The registration approval statistics that were mentioned in this article are not the only reason for the ZaZiBoNa collaborative initiative's success. The response time from the ZaZiBoNa collaborative initiative is around 9 months which highlights efficiency and effectiveness in the review process when compared to other SADC countries. It also highlights the efficiency with regards to GMP inspections. Each country would have to conduct individual GMP inspections if they were not part of the ZaZiBoNa joint collaborative initiative thereby costing the NMRAs more financial resources as these inspections are not funded by the pharmaceutical industry. The joint GMP inspections help with being cost-effective and efficient as NMRAs can spend resources (both human and financial) on other projects.

The literature that has been reviewed has not provided any insight into what major stakeholders such as RAPs and regulators think about the harmonisation initiatives in SADC. This study aims to bridge that gap and gain an understanding of the perceptions of regulators and the pharmaceutical industry in South Africa with regard to harmonisation. The section that follows details what literature has revealed as some of the major advantages and disadvantages of and barriers to harmonisation.

2.10 BENEFITS OF REGULATORY HARMONISATION

Numerous advantages of harmonisation have been described in literature. These advantages have had a positive effect on NMRAs, the pharmaceutical industry, and consumers. There is greater alignment of industry submission practices (WHO, 2014a). The CTD is a format for medicines registration applications that has helped facilitate more efficient review processes and has allowed for electronic submission (Singh, 2015). This has resulted in a reduction in workload which translates into improved regulatory performance (Azatyan, 2013).

Harmonisation has helped to reduce duplication of clinical trials and has shortened drug development timelines (Valverde, 2015). The cost of development of new drugs has decreased as a result of reduced regulatory documentation requirements translating into lower prices (WHO, 2008). There is increased competitiveness as a result of companies being able to enter more markets with a single submission (WHO, 2008). This may increase price competition amongst manufacturers, resulting in lower prices for consumers.

The joint review of dossiers as a result of harmonisation and collaboration have resulted in shortened approval timelines (Ndomondo-Sigonda *et al.*, 2018). There is greater access to essential medicines as a result of shortened approval timelines (WHO, 2008). Harmonisation has also helped to direct expertise to areas that improve public health and increase access to

essential medicines (Azatyan, 2013). A greater variety of generics have been made available that may have previously not been registered in certain markets (WHO, 2014a). Harmonisation has therefore resulted in improved public health (Azatyan, 2013) as a result of greater access to essential medicines, new medicines, and generics. Despite the many benefits of harmonisation many countries are still struggling to reap the full benefits of harmonisation as a result of the disadvantages.

2.11 DISADVANTAGES OF REGULATORY HARMONISATION

The variance in technical expertise amongst regulators at NMRAs in Africa have resulted in harmonisation progressing at different speeds in different countries (WHO, 2014a). The variable interest in harmonisation across countries in Africa, combined with a lack of institutional frameworks at regional level to drive harmonisation (Kamwanja *et al*., 2010), makes it difficult to reap the full benefits of the process. Most NMRAs in Africa do not have adequate resources to perform the major regulatory functions (Azatyan, 2013). NMRAs are at different levels of economic development and some lack the financial and human resources required to participate in regulatory harmonisation (Kamwanja *et al*., 2010). The lack of resources severely hampers assessment of registration dossiers, thereby causing delays in medicines reaching the market (Azatyan, 2013). There is limited transparency of the registration process in Africa, thereby leading to erratic review timelines (Azatyan, 2013). These are some of the issues that SADC NMRAs are facing, whereas other markets have not been able to implement harmonisation initiatives because of the many barriers that exist as detailed in Section 2.12.

2.12 BARRIERS TO REGULATORY HARMONISATION

Many countries wish to maintain their sovereignty with regards to registration or rejection of a product application, making it more difficult for harmonisation to progress (Sithole *et al*., 2020). There are differences in the assessment of medicine applications between countries in SADC and bias exists based on local population needs (Calder, 2016). There is great complexity involved in setting up and maintaining a collaborative review system for harmonisation (WHO, 2014a). The lack of political will in governments and a lack of relationships between countries have created barriers to harmonisation (Calder, 2016). Some NMRAs are not familiar with the regulatory systems of other NMRAs (WHO, 2014a). The language barriers between countries and different labelling legislation also pose problems for harmonisation (Sithole *et al*., 2020).

Literature has revealed numerous benefits and disadvantages of and barriers to harmonisation. The benefits that have been identified in literature sources that were reviewed for this study show that these outweigh the barriers and disadvantages as described above. This study aims to find out whether major stakeholders such as RAPs and regulators have identified any new benefits or disadvantages of or barriers to harmonisation as a result of the newly implemented SAHPRA guidelines and after participation in the ZaZiBoNa collaborative initiative. NMRAs should be aware of these benefits, disadvantages, and barriers prior to adopting harmonisation initiatives.

2.13 CONCLUSION

History has shown that medicines regulations are vital to ensure the quality, safety, and efficacy of medicines. The use of medicines that are of poor-quality, safety, and efficacy can lead to death, worsening of the condition, or resistance, which will result in consumers losing trust in

the healthcare system (WHO, 2003). There also needs to be an effective NMRA in countries to ensure that medicines are regulated appropriately. Many developing countries lack resources (both human and financial) to effectively regulate medicines (WHO, 2008). South Africa is one of the countries that realised that its NMRA was ineffective in executing its function, hence a new NMRA was established. This NMRA has now adopted a reliance-based review procedure to help accelerate registration approvals. This study aims to identify whether major stakeholders such as RAPs and regulators perceive that the new SAHPRA guidelines will be beneficial to them by increasing access to essential medicines, improving registration approval timelines, and increasing efficiency in the workplace

The trend seems to be that more and more countries are adopting harmonisation initiatives globally and in Africa. The ZaZiBoNa collaborative initiative has shown great successes in the SADC region. Literature has failed to provide insight into how major stakeholders feel about the pace at which harmonisation is progressing in SADC, at which new medicines are being registered in SADC, at which new medicines are reaching the market in SADC. These aspects are important to understand as they highlight efficiencies and inefficiencies in the current process. The efficiencies can be shared with other regions while the inefficiencies can be addressed.

The harmonisation of medicines regulations has definite benefits, disadvantages and barriers. Literature has provided great insight into the benefits and disadvantages of and barriers to harmonisation. This study builds on what is already known and aims to capture new barriers, disadvantages, and benefits or recurring themes that align with that found in literature. The benefits and disadvantages of and barriers to harmonisation are important to understand so that regions that want to adopt harmonisation can know what to expect. They can also weigh the advantages against the disadvantages to see if harmonisation would be feasible in their region.

For regions that have already adopted harmonisation initiatives, the barriers would illustrate areas that need improvement.

This study aims to understand the RAPs and regulators' perspectives on the new SAHPRA guidelines and the impact of these guidelines on efficiency. The perspectives of major stakeholders are important to understand as this provides a good indication of how supportive and collaborative the stakeholders will be with regards to harmonisation initiatives. This study also gauges how major stakeholders feel about the efficiency of SADC harmonisation initiatives. This helps to identify any shortcomings in the process that can be addressed to improve the process or it can highlight major efficiencies that other regions may want to leverage. This study elicits perceptions of the current advantages, disadvantages, and barriers that major stakeholders are faced with as a result of harmonisation. The advantages can be used to promote harmonisation in regions that have not yet adopted these initiatives. The barriers to harmonisation can show NMRAs what needs to be worked on to improve current systems and processes.

CHAPTER 3
METHODOLOGY

3.1 INTRODUCTION

As mentioned previously, the main objectives of this study was to gauge the perceptions of the pharmaceutical industry and regulators in South Africa on the effect that harmonisation has had on their efficiency in the workplace, registration approvals, access to essential medicines, and the benefits for major stakeholders. It had also determined whether the pharmaceutical industry and regulators are satisfied with SADC harmonisation initiatives and the speed at which new medicines are reaching the market in SADC. The study identified new benefits and disadvantages of and barriers to harmonisation initiatives. The methodology to achieve the aims and objectives is presented in this chapter.

3.2 STUDY DESIGN

This study was a cross-sectional study design which utilised mixed research methods to analyse data. The results from quantitative methods are more reliable. However, it is difficult to get an in-depth understanding of the participants' feelings and perceptions (Rahman, 2016). The qualitative methods were therefore used to analyse the open-ended questions in an effort to elicit perceptions of and feelings and attitudes towards harmonisation. The qualitative methods have also helped to support the quantitative method findings.

Appendix A contains a copy of the survey questionnaire. The survey was piloted on five individuals from various multinational pharmaceutical companies across South Africa, as well as four regulators from SAHPRA with technical expertise. A survey was selected as an appropriate method for data collection as it produces empirical data and provides a large amount of data in a short period while still being economical (Kelley, Clark, Brown & Sitzia,

2003). A survey was easier to distribute to large numbers of pharmaceutical representatives and regulators across the country, thereby increasing the accuracy, validity, and reliability of the results (Noor, 2008). It also allowed for participants to complete the survey in their own time. The survey had the option for participants to save their answers and return to the survey to pick up where they left off. The survey could also be more widely distributed than other data collection methods.

Face-to-face interviews were not an option, because of the lockdown during the COVID-19 pandemic. Since there were so many pharmaceutical industry personnel and regulators across the country, it would be too time-consuming to conduct face-to-face or telephonic interviews. Regulatory industry personnel and regulators may also not have the time available to participate in face-to-face or telephonic interviews.

The disadvantage of circulating a survey is that participants may forget to complete the survey. It is for this reason that a reminder was sent out two weeks after the initial survey invitation. Surveys may also get lost in the numerous daily emails that participants get or may even land in participants' spam folders. Other methods such as telephonic interviews may be more useful. However, due to the large sample size and time limitations, the survey was a better option. In the COVID-19 period, the survey was the quickest way to reach all participants in the shortest period of time.

3.2.1 Study Population

The population of interest for this study were professionals in the pharmaceutical industry who may be impacted by harmonisation initiatives, as well as regulators from SAHPRA. The professionals in the pharmaceutical industry include RAPs and the heads of regulatory affairs. The inclusion criteria for other professionals in the pharmaceutical industry were those who

had knowledge of harmonisation initiatives and those who were directly impacted by harmonisation, such as responsible pharmacists. Participants were able to choose which role best describes their current position. The options were regulators, regulatory affairs professionals or other. The "other" category was vetted by the author to remove participants that were not directly impacted by harmonisation. For those individuals that formed part of the "other" category that may have been directly impacted by harmonisation but answered "no" to the questions regarding awareness of the amendments to the Medicines and Related Substances Act (Act 101 of 1965) and the harmonised guidelines that SAHPRA had adopted were excluded from the study. This is because if one is a responsible pharmacist in the South African pharmaceutical regulatory industry, they should be aware of these changes. The inclusion criteria for the regulators were only regulators with technical experience. All administrative SAHPRA staff were excluded from the study as they are likely to not have enough experience on the topic.

3.2.2 Sampling Technique

It was not possible to test the entire population of the pharmaceutical industry and regulators in South Africa. A sample must be selected that will be representative of the population (Sharma, 2017). The sampling method employed in this study gave each member of the population an equal chance of being selected to participate in the study. This was regarded as a fair way to obtain a sample as every member of the population had an equal chance of participating (Sharma, 2017).

The survey questionnaire was distributed via the Southern African Pharmaceutical Regulatory Affairs Association (SAPRAA), South African Association of Pharmacists in Industry (SAAPI), Self-medication Manufacturers Association of South Africa (SMASA), Generic and

Biosimilar Medicines of Southern Africa (GBMSA), and the Innovative Pharmaceutical Association of South Africa (IPASA). SAPRAA provides most RAPs in South Africa an equal opportunity to participate in the study, as its members are mainly RAPs. SAAPI sent the survey to all their members who are pharmacists in the pharmaceutical industry. SMASA sent the survey to its members who manufacture and register over-the-counter medicines. IPASA sent the survey to its members who manufacture and register innovator medicines. GBMSA sent the survey to its members who manufacture and register generic products. SAHPRA distributed the survey to all technical staff at SAHPRA, which covers the entire population of regulators. This covers almost all avenues to reach SAHPRA, innovator companies, generic companies, consumer companies, the pharmaceutical industry, and RAPs. There was a chance that the survey did not reach all professionals in the pharmaceutical industry if they did not belong to the industry associations mentioned above.

3.2.3 Sample Size

The sample included 263 participants from the pharmaceutical industry. This represented 31.72% of the pharmaceutical industry that may have been directly or indirectly impacted by harmonisation. The sample size was calculated using a Raosoft® sample size calculator. The population size for the pharmaceutical industry was 829 with a margin of error of 5% and confidence interval of 95% using the estimated response distribution of 50%. The sample size for regulators could not be calculated as responses were not received from SAHPRA regarding the population size.

3.3 NATURE OF THE QUESTIONNAIRE

The research questionnaire was peer-reviewed by regulatory affairs professionals and a few SAHPRA regulators. The questionnaire comprised of 32 questions, which took approximately 15 minutes to complete. The questionnaire was divided into Part A for South African harmonisation initiatives and Part B for SADC harmonisation initiatives. Most of the answers were in the form of a Likert scale. However, there were also open-ended questions and yes/no answer options. Part A focused on South Africa harmonisation initiatives and sought to understand whether the participants were aware that the Medicines and Related Substances Act (Act 101 of 1965) had been amended and new SAHPRA guidelines had been issued. If they were aware that SAHPRA issued new harmonised guidelines they could then proceed with Part A, if not they were diverted to Part B. The questions in Part A focused on whether harmonisation would increase efficiency in the workplace, whether it would benefit regulators, consumers, and the pharmaceutical industry and whether it would improve registration timelines. The questions in Part B focused on the ZaZiBoNa collaborative initiative and whether it would improve registration timelines, increase access to essential medicines, and improve efficiency in the workplace. There were also questions focused on how easy it is to access information on ZaZiBoNa and what some of the primary sources of ZaZiBoNa information are. A few questions were aimed at determining how satisfied participants were with the rate at which medicines are reaching the market in SADC, at which harmonisation activities are progressing in SADC, and at which medicines are being registered in SADC. There were also three open-ended questions that sought to find out the advantages and disadvantages of and barriers to harmonisation initiatives.

3.3.1 Pilot Study

The chief executive officer (CEO) of SAHPRA was contacted via email to explain the research project and to receive approval to conduct the study within SAHPRA. Approval from the SAHPRA CEO was obtained in June 2020 via email. The pilot survey was then circulated via a weblink to one SAHPRA representative who forwarded it to four of his colleagues in June 2020. Regulators were given fourteen days to respond to the pilot study. A reminder was sent out seven days after the initial pilot survey had been circulated. The reminder was sent out via email via the SAHPRA representative.

Five individuals from different multinational companies were contacted via email or phone to discuss the research project. These individuals were excluded from the study. The pilot study was distributed via email to everyone at the end of May 2020. A reminder was sent out seven days after the initial email in June 2020 to remind participants to complete the pilot questionnaire.

The questionnaire was piloted to determine whether the questions were clear and easily understood. A member of SAHPRA pointed out that the title of the research is ambiguous as it talks about African medicines, which can be confused for traditional medicines. The title was not amended, but the SAHPRA official was contacted to provide further clarity. The questionnaire was then divided into two parts, with one part specifically dedicated to South African harmonisation initiatives and the other part dedicated to SADC harmonisation initiatives, with specific focus on ZaZiBoNa, which forms part of the ARMHI. A preamble was added to explain what ZaZiBoNa was. Some respondents in the pharmaceutical industry were not too familiar with the concept of ZaZiBoNa and hence a preamble was useful and there was reference to the website that they could visit for more information. One respondent advised

that it would be better to obtain more than one advantage, disadvantage, and barrier to harmonisation. The questionnaire was amended accordingly.

3.3.2 Data Collection

An online survey was created using Survey Monkey. The weblink to the survey was circulated to regulators with technical expertise at SAHPRA via an email from their SAHPRA colleague on 1 July 2020. The same weblink was circulated to RAPs via an email through the SAPRAA, SAAPI, SMASA, GBMSA, and IPASA on 1 July 2020. Confirmation was received from all industry associations that the survey was disseminated. Reminders were sent out fourteen days after the initial email to invite people to complete the survey. SAPRAA had provided further feedback on the number of recipients that were mailed. SAHPRA had also confirmed that they disseminated the survey and sent follow ups. The channels through which the link to the survey was disseminated gave all pharmaceutical industry professionals and regulators a fair opportunity to participate in the study.

3.3.3 Ethical Considerations of Data Collection

Participation in the study was voluntary and participants could decline to participate without being penalised. Anonymity of participants was maintained as no information that could identify an individual was collected.

3.4 STATISTICAL CONSIDERATIONS

The survey mainly utilised Likert-type rating scales to ascertain the attitudes and perceptions of the target population. This scale produces an ordinal level of measurement (Jamieson, 2004).

Once the survey was closed the responses to each question was downloaded from SurveyMonkey. The data was manually prepared prior to analysis to detect missing data and outliers using Microsoft Excel. SPSS statistics software was used to analyse the data. The number of responses per question was converted to a percentage. This percentage was plotted or described against each question on a bar graph, pie chart or a table. These show the number of responses received as a percentage for each category of answer as per the options on the Likert scale. The open-ended questions were analysed using axial coding to identify recurring patterns and themes or sub-themes that relate to the study objectives.

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3.5 RELIABILITY AND VALIDITY OF THE RESEARCH INSTRUMENT

The research instrument had to be reliable and valid to ensure that the findings obtained from this study are free from error (Tavakol & Dennick, 2011). Validity determined whether the survey measures what it was intended to measure (Tavakol & Dennick, 2011). The research questionnaire demonstrated content validity as it adequately covers all areas of the research objectives (Taherdoost, 2016). The extensive literature review helped to extract relevant information to develop the questionnaire to ensure that the content was valid. The questionnaire was also piloted on experts within the field of regulatory affairs and regulators at SAHPRA to help ensure that it was clear, concise, and unambiguous. Amendments were made to the questionnaire in line with expert recommendations in order to further strengthen the validity of the research instrument.

The reliability of a research instrument was also essential. However, it has to be combined with validity (Taherdoost, 2016). Reliability is the ability of the research instrument to measure consistency (Heale & Twycross, 2015). Cronbach's alpha coefficient is the most commonly utilised measure for internal consistency (Taherdoost, 2016). Cronbach's alpha coefficient was

used to determine the reliability of the research instrument (Tavakol & Dennick, 2011). The Cronbach's alpha result is a number between 0 and 1; any score above 0.7 is acceptable for reliability (Heale & Twycross, 2015). Cronbach's alphas above 0.7 indicate that grouped questions with a similar response scale are well-related enough to form a single variable.

CHAPTER 4
RESULTS AND DISCUSSION

4.1 INTRODUCTION

The survey generated a total of eighty-eight responses from professionals in the pharmaceutical industry. The response rate was 10.62%, which is lower than 36.83%, which is the mean response rate for electronic surveys (Sheehan, 2001). After the data was cleaned, it was found that only forty-nine responses could be utilised in the analysis as a result of thirty-nine respondents leaving questions unanswered. There were thirty-four cases that were excluded because there were no responses from the respondents with the exception of demographic responses. There were five cases that had less than four responses to the entire questionnaire. The cut-off point for the exclusion of survey responses were the absence of actual responses outside of the demographic questions. The survey was aimed at both professionals in the pharmaceutical industry in South Africa and regulators at SAHPRA. The survey generated no responses from any of the regulators at SAHPRA. Numerous reasons could be put forward for this, including the COVID-19 pandemic which kept regulators very busy evaluating registrations pertaining to this pandemic. The regulators were also busy evaluating backlog submissions that the pharmaceutical industry had to resubmit in various windows during the course of the year. There was a follow-up with the SAHPRA to determine why no responses were received to the survey questionnaire. However, no answer was received.

4.2 RESPONDENTS' CURRENT POSITIONS IN THE PHARMACEUTICAL INDUSTRY

The questionnaire was aimed at regulators at SAHPRA with technical experience and first-hand experience of harmonisation, as well as professionals in the pharmaceutical industry who have been directly or indirectly affected by harmonisation initiatives. Questionnaires from 49

respondents were analysed. Figure 4.1 shows the distribution of the sample by their current role in the pharmaceutical industry in South Africa. Of the respondents, forty-one (83.7%) were RAPs in the pharmaceutical industry and eight (16.3%) were classified as "Other". Those not RAPs constituted one respondent who worked in medicines marketing, one who worked in validation, and one who was responsible for acquisitions and sale of product dossiers. Five were responsible pharmacists. The sample was, therefore, dominated by respondents who are RAPs. They are, as expected, close to the subject matter of the study and were the target sample for this study. All of the respondents who have other roles were included in the data analysis as they had knowledge of South African harmonisation initiatives and SADC harmonisation initiatives.

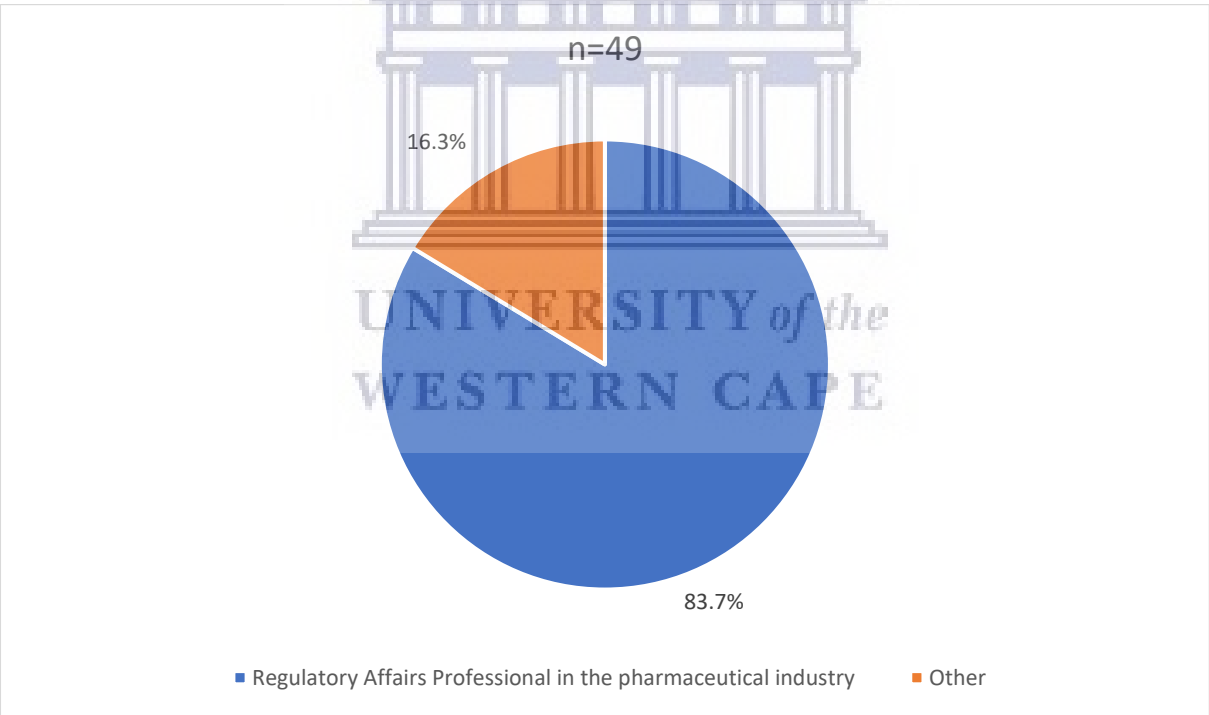

Figure 4.1: Distribution of Respondents according to their Current Role in the Pharmaceutical Industry

4.3 HARMONISATION INITIATIVES IN SOUTH AFRICA

4.3.1 Awareness of Harmonisation-related Changes that have been adopted in South Africa

The first section of the questionnaire addressed harmonisation activities in South Africa, with specific focus on the new guidelines that have been adopted and implemented by SAHPRA. Of the forty-nine respondents, 87.8% were aware of the amendments made to the Medicines and Related Substances Act (Act 101 of 1965) with relation to harmonisation (as shown in Figure 4.2). A relatively small percentage (12.2%) of the respondents were not aware of these amendments. Most of the participants (89.8%) were aware that SAHPRA had recently adopted harmonised guidelines for certain regulatory activities. This illustrated that most of the participants were suitable research contributors based on their awareness of harmonisation-related changes in South Africa. A minority, i.e. 12.2%, were not aware of the amendments to the Medicines and Related Substances Act (Act 101 of 1965). The Medicines and Related Substances Act does not specifically mention harmonisation initiatives but rather includes a section on the interaction and communication between SAHPRA and other regulatory authorities. This is related to the reliance-based methods of evaluation that SAHPRA is utilising. Reliance, as defined by the WHO, is an act whereby one NMRA fully or partially relies on an assessment carried out by another NMRA to make a decision (WHO, 2020a). The 10.2% of participants who were not aware of SAHPRA's harmonised guidelines skipped over the questions related to SAHPRA's guidelines and moved directly to Part B's SADC harmonisation questions.

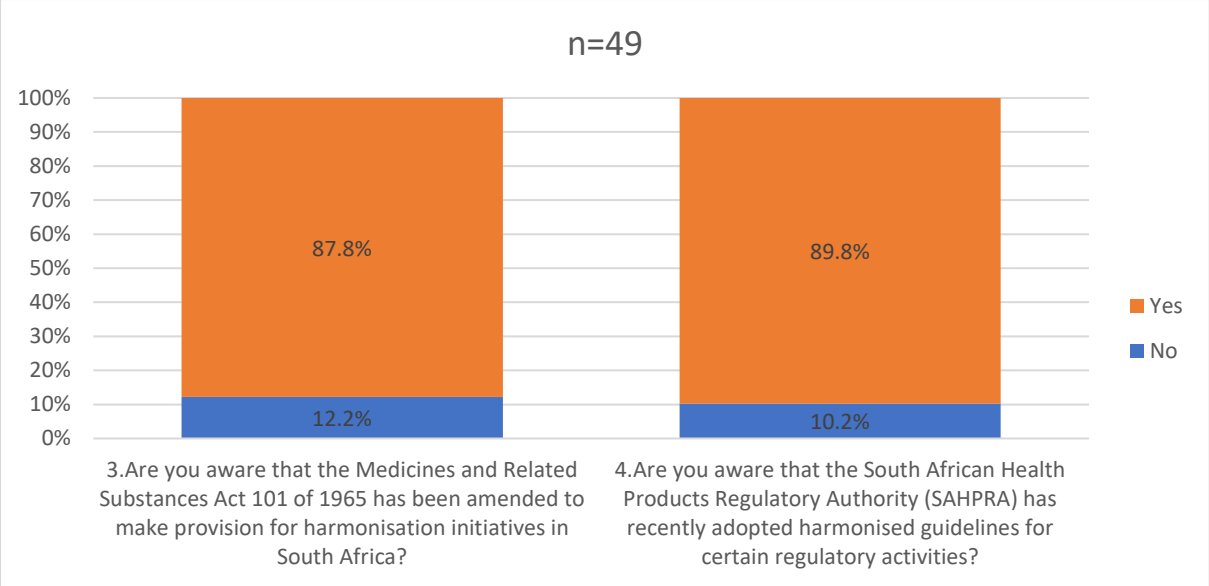

Figure 4.2: Respondents' Awareness of Harmonisation-related Changes that have been adopted in South Africa

4.4 THE EFFECT OF SAHPRA'S HARMONISED GUIDELINES ON EFFICIENCY

The participants' responses to the potential effect of the harmonised SAHPRA guidelines on their work efficiency, as well as the effect on registration approvals timelines of essential medicines, NCEs, and generic medicines as a result of SAHPRA's reliance-based evaluation system are presented in Table 4.1. A Cronbach's alpha result of 0.869 was attained for the four questions in Table 4.1, indicating that these factors reliably represent efficiency.

Table 4.1: Respondents' Perceptions of Increased Efficiency in the Workplace and Speed of Registration Approvals

Efficiency	Nr of Responses	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
5. Guidelines will likely result in increased efficiency in your current line of work	41	2.4%	9.8%	26.8%	56.1%	4.9%
7. Guidelines will likely result in faster registration approvals of essential medicines	28	3.6%	7.1%	28.6%	53.6%	7.1%
9. Guidelines will likely result in faster registration approvals of NCEs	28	3.6%	10.7%	35.7%	42.9%	7.1%
11. Guidelines will result in faster registration approvals of generic medicines	44	2.3%	6.8%	25.0%	59.1%	6.8%

* Cronbach's alpha = 0.869

4.4.1 Efficiency in Respondents' Current Line of Work

The modal response to the question whether "The newly adopted harmonised SAHPRA guidelines will likely result in increased efficiency in your current line of work?" was "Agree" with a 56.1% frequency. This was followed by "Neutral" with 26.8% frequency. More than half of the participants (61%) (56.1% "Agree" and 4.9% "Strongly agree") believe that the harmonised SAHPRA guidelines will increase their work efficiency. A minority of respondents believe that efficiency will remain the same. The open-ended questions revealed that eighteen respondents who agreed or strongly agreed did so because they believe that the adoption of the harmonised SAHPRA guidelines will result in the streamlining of current processes to reduce duplication of activities in different countries, and the simplification of processes with learning and input from other countries with the use of a common standardised approach. The reasons such as streamlining of processes and reduction in duplication of efforts given by respondents are in line with those described in literature (Azatyan, 2013; WHO, 2014a). Respondents had pointed out that the harmonisation of SAHPRA guidelines with the EU guidelines had resulted in them having received quicker responses to regulatory submissions from SAHPRA, thereby highlighting efficiencies at SAHPRA. Respondents also highlighted that being able to utilise approvals from RRAs has helped to expedite reviews at SAHPRA, thereby resulting in faster approval timelines. It was interesting to note that among those who were neutral, the common narrative was that the old SAHPRA guidelines and processes are not to blame for registration delays but rather people and their attitudes. These respondents believe that changing the processes will not result in an automatic improvement in efficiency at SAHPRA.

The 12.2% of respondents who disagreed (9.8% "Disagree" and 2.4% "Strongly disagree") believe that SAHPRA, as an implementing party, had introduced numerous additional requirements that were time-consuming and caused a bit of uncertainty of what was actually required. The respondents felt that it was difficult to access these new harmonised guidelines.

The respondents also indicated that harmonisation should help to save regulators' time, but this will not be the case if regulators do not change their ways of evaluation. The implementation of additional requirements to support the new guidelines was noted by at least six respondents as having the potential to increase workload and lead to reduced efficiency among employees. Three respondents highlighted the fact that SAHPRA still requires several additional templates to be filled in for products that have already been registered by RRAs, thereby affecting efficiency. One participant said that the new guidelines are more complex and unclear. Another mentioned that SAHPRA should release a guideline that summarises the main requirements similar to what the MCC had in the past. One respondent mentioned that the newly adopted addendum to the variation guideline is more stringent and requires the submission of a minor manufacturing change before implementation, which can delay the manufacturing process.

4.4.2 Faster Registration Approval of Essential Medicine

The modal response to the question regarding faster registration approvals of essential medicines was "Agree", chosen by 53.6% respondents, followed by "Neutral", selected by 28.6%. Overall, 60.7% of the respondents were agreeable to the statement (53.6% "Agree" and 7.1% "Strongly agree"). The majority of respondents were confident that the harmonised SAHPRA guidelines will improve the time it took for the registration of essential medicines, although a sizeable proportion of respondents (28.6%) also believe that registration efficiency will remain unchanged. Six participants felt that the new harmonised guidelines or new evaluation pathways will not affect timelines. Among the respondents who agreed, the main reasons given were that harmonisation will shorten review timelines and result in fewer information requirements, and that the reliance model will facilitate an improved rate of registration of essential medicines. Three respondents also stated that they had agreed simply because they are not sure how the whole system will work. SAHPRA will be utilising the WHO PQP assessments for a reliance-based review (SAHPRA, 2019a). The WHO PQP prequalifies

certain essential medicines (WHO, 2020b). Hence, this should result in faster approvals of certain essential medicines at SAHPRA. Among the respondents who felt neutral, four respondents stated that there is no evidence that harmonisation will change the rate of registration for essential medicines. Three participants doubted SAHPRA's abilities in the implementation process and believed that this made it difficult to foresee improved efficiency in the registration of essential medicines. The main reason cited for their concern was a lack of human resources at SAHPRA. This is not in line with what was reported by the DOH in 2018 and Keyter *et al.* (2018a), who reported that staffing at SAHPRA would no longer be a concern, as SAHPRA would rely on external experts until in-house staff were adequately upskilled (DOH, 2018). SAHPRA also aims to ensure that it has enough skilled individuals to carry out regulatory functions (Keyter *et al.*, 2018a).

From the responses received in the open-ended question, it is clear there is a perception that the registration of essential medicines would be faster if the implementation of harmonised guidelines is thoroughly conducted, although a few respondents doubted that the implementation will be smooth.

4.4.3 Faster Registration Approval of NCEs

There were twenty-eight valid responses to determine respondents' perception of whether the harmonised SAHPRA guidelines will likely result in faster registration approvals of NCEs. Of these responses, 42.9% agreed that SAHPRA guidelines will likely result in faster registration approvals of NCEs, followed by 35.7% who remained neutral. This highlights the view that there is no strong consensus on the view that the changes will result in faster registration approvals of NCEs.

The respondents who agreed with the statement gave reasons that are similar to the previous two questions' answers for why they believe the rate of new approvals will increase. The participants mentioned that the removal of duplications and the availability of more information to all stakeholders will likely lead to faster registrations. These reasons for believing that registration approval of NCEs will increase are associated with those of increased collaboration and decreased duplication of activities cited in literature (Azatyan, 2013; WHO, 2013). Respondents who were neutral maintained that there is no evidence or indication that there will be improvements in the registration process and that, in practice, SAHPRA is likely to face implementation challenges that will make it difficult to realise efficiencies. They believe actual efficiencies will depend on the cooperativeness of health authorities in other countries. Kamwanja *et al.* (2010) mentioned that there was variable interest in harmonisation in different countries, which may have led to a lack of cooperation between NMRAs, as discussed by respondents. Respondents who disagreed with the statement gave similar reasons to the neutral cluster, adding the view that NCEs require an in-depth review and regulators in SADC may not have the experience to evaluate NCEs. This is in line with the WHO publication that identified the lack of technical expertise at NMRAs as a challenge to the review process (WHO, 2014a). Thus, on this efficiency-related question, the saturation point was reached as the sample generally did not give any new reasons as to why they agreed with the given statements.

4.4.4 Faster Registration Approval of Generic Medicines

There were forty-four responses to the question with respect to whether SAHPRA's harmonised guidelines will result in faster registration of generic medicines. It was shown that 59.1% of these respondents agreed that the newly adopted harmonised SAHPRA guidelines

will result in faster registration approvals of generic medicines, followed by 25% of these respondents who remained neutral. Overall, the majority of respondents (65.9%) (59.1% "Agree" and 6.8% "Strongly agree") were agreeable to the statement, indicating more positivity toward and consensus on the likelihood of the harmonised SAHPRA guidelines to improve efficiency in the registration of generic medicines. Those who agreed or strongly agreed with the statement generally believe that the elimination of duplication, the increased availability of information, and the use of the reliance model for evaluations will result in faster registration approvals for generic medicines.

In the neutral cluster, respondents' choice was driven by three broad perceptions:

- a lack of knowledge and certainty on how the process will improve registration speed,
- scepticism on the implementation abilities of SAHPRA, and
- the view that the process relies on external parties.

One participant highlighted that companies that only register medicines in South Africa are not likely to be affected by SAHPRA's newly adopted harmonised guidelines and evaluation methods. This is because they are unable to utilise reliance-based evaluation for the registration of medicines.

4.5 BENEFITS OF THE NEWLY ADOPTED HARMONISED SAHPRA GUIDELINES

In this subsection, three questions were analysed to determine respondents' perceptions of the benefits of the newly adopted SAHPRA guidelines for major stakeholders. Table 4.2 depicts the responses to these questions regarding the benefit of harmonisation for major stakeholders. A Cronbach's alpha of 0.88 was calculated for the below questions, demonstrating that these reliably represent respondents' perceptions.

Table 4.2: Respondents' Perceptions of the Benefits of Harmonisation for Major Stakeholders

Benefits	Nr of Responses	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
13. Guidelines will ultimately benefit the public	43	2.3%	2.3%	20.9%	55.8%	18.6%
15. Guidelines will benefit regulators	37	0.0%	2.7%	10.8%	64.9%	21.6%
17. Guidelines will benefit the pharmaceutical industry	44	0.0%	2.3%	15.9%	68.2%	13.6%

* Cronbach's alpha = 0.88

4.5.1 The Benefits of Harmonisation for the Consumer

In total, 74.4% of the forty-three respondents agreed (55.8% "Agree" and 18.6% "Strongly agree") that the newly adopted harmonised SAHPRA guidelines will ultimately benefit the public. Another 20.9% of the respondents were neutral on this view. Almost all the respondents from the agreeing cluster who answered the open-ended question relating to this view believe that the public will benefit from SAHPRA's harmonisation initiatives through speedier access to new medicines. Three respondents believe that the cost of access could also benefit the public. Five participants believe that the public will benefit through increased choice of medicines available on the market. Literature has discussed the improved approval timelines (Ndomondo-Sigonda *et al.*, 2018) as a result of greater efficiencies, which will ultimately increase the variety of medicines available on the market (WHO, 2014a), thereby benefiting consumers, as discussed by respondents. The decrease in duplication of clinical trials (Valverde, 2015) will help to decrease the cost of drug development (WHO, 2008), which could translate into reduced costs for consumers.

Within the neutral cluster, the main reasons given for maintaining neutrality on the view that the newly adopted harmonised SAHPRA guidelines will ultimately benefit the public were that

the benefits will only accrue to the public if the review process itself is shortened and if SAHPRA does not request additional documents when products are registered by RRAs. The remaining neutral respondents were neither confident nor unconfident about the change process.

Finally, within the disagreeing cluster, respondents gave two main reasons for their choice of answer. They believe that SAHPRA's evaluation processes are still inadequate to meet market needs and that harmonisation alone will not resolve much. Another reason for disagreeing with this statement was that SAHPRA has not committed to timelines for approval and there are additional costs involved in registration, which may be passed onto the consumer. New regulations regarding SAHPRA's fee structure have been gazetted and the cost of registration has increased significantly from the previous fee structure (DOH, 2020). This may in turn mean greater costs for the public as mentioned by respondents.

4.5.2 The Benefits of Harmonisation for Regulators

Out of the thirty-seven respondents who answered, 64.9% agreed and 21.6% strongly agreed that the newly adopted harmonised SAHPRA guidelines will benefit regulators. Only 12.5% (10.8% "Neutral" and 2.7% "Disagree") did not agree with this view. Within the agreeing cluster (86.5%), the main reasons forwarded were that workload for regulators will be greatly reduced. Regulators will be able to rely on assessments carried out by RRAs, thereby decreasing their workload. With the reliance model there will be no need for regulators to perform a full review of every product dossier. They can simply utilise the reliance-based evaluation pathways to speed up the review process. Other reasons given were that there will be better communication and increased information flow amongst regulators in different regions which could improve the quality of their reviews. The recurrent themes of duplication elimination and timeous response were mentioned by numerous participants. These responses

are linked to the fact that regulators are able to utilise assessment reports from RRAs, meaning that the quality of reviews should increase and timelines for approval will decrease as a result of work-sharing and a reduction in duplication of efforts. These reasons are in line with those discussed in literature with regards to decreased workload (Azatyan, 2013) as a result of increased collaboration and work-sharing (WHO, 2013).

The neutral cluster's responses were characterised by the view that regulators will only benefit from harmonisation "if they accept reports from other authorities and stop requesting unnecessary information". One respondent stated that harmonisation will only benefit regulators if SAHPRA works together with RRAs and does not adopt unified approaches to certain guidelines such as the EU variations guideline. Literature has highlighted that some countries in SADC wish to maintain sovereignty (Sithole *et al*., 2020), which is in line with respondents' perceptions of why regulators may not fully benefit from SAHPRA's harmonised guidelines.

The disagreeing cluster's responses had the same themes: that harmonisation might not work well because the current SAHPRA staff do not fully appreciate the processes involved in evaluation and this lack of knowledge might affect the post-harmonisation phase, denying regulators the potential benefits of the process.

4.5.3 The Benefits of Harmonisation for the Pharmaceutical Industry

There were forty-four respondents, of whom 81.8% agreed (68.2% "Agree" and 13.6% "Strongly agree") that the newly adopted harmonised SAHPRA guidelines will benefit the pharmaceutical industry. Of the forty-four responses, 2.3% of respondents that did not agree and 15.9% were neutral to this view. In addition to the regular reasons, i.e. faster registrations, reduced workload, the elimination of duplication, and increased access to medicines, that were

discussed as potential benefits of adopting harmonised guidelines, respondents also gave unique responses – specifically that the new processes will reward innovators who do not have to suffer from increased bureaucratic processes. As described in literature, there would be a decrease in drug development timelines (Valverde, 2015) and a reduction in drug development cost as a result of harmonisation (WHO, 2008). The regulatory industry will benefit from faster approvals and this will help to boost manufacturers' sales of new products. Drug manufacturers are able to enter more markets with a single submission (WHO, 2008). The changes will also help to curb the illegal distribution of medicines. This would help to improve public health, as described in literature (Azatyan, 2013). Another respondent believed that harmonisation would open up opportunities for investment in the South African pharmaceutical industry as investors value convenience in the registration process. One respondent who disagreed believes that the industry will not benefit from any of the changes, at least in the short term.

4.6 HARMONISATION INITIATIVES IN SADC

4.6.1 Perceptions of whether ZaZiBoNa will improve Registration Timelines in SADC

Out of forty-seven responses, 68.1% agreed (63.8% "Agreed" and 4.3% "Strongly agreed") that medicines registration harmonisation initiatives such as the ZaZiBoNa collaborative initiative will ultimately improve registration timelines in SADC. Of the forty-seven responses, 25.5% were neutral to this view while 4.3% disagreed with it. The reasons cited for these responses were attributed to less duplication of effort for regulators, dossiers not having to be reworked into different formats, and work-sharing amongst regulators resulting in abbreviated reviews of new products. The recurring themes highlighted by respondents align to those mentioned in literature (Azatyan, 2013; WHO, 2013). Respondents however did not allude to capacity building at under-resourced NMRAs that may also help improve registration timelines

(Sithole *et al*., 2020). Capacity building at NMRAs will help with faster registrations thereby making staff turnover issues that some NMRAs face have minimal effect on registration timelines. All 25.5% of the neutral respondents were not sure whether there will be any improvement in registration timelines. Within the disagreeing cluster, there were views that under ZaZiBoNa, each country will still maintain a level of independence which may affect the improvement of registration timelines.

4.6.2 Perceptions of whether ZaZiBoNa will increase Access to Essential Medicines in SADC

Among the responses, 72.9% (64.6% "Agree" and 8.3% "Strongly agree") held the view that medicines registration harmonisation initiatives such as the ZaZiBoNa collaborative initiative will increase access to essential medicines in SADC. The remaining responses (27.1%) were neutral to the view. In total, there is a common view that the initiative will increase access to essential medicines in the region. Respondents in the agreeing cluster forwarded reduced timelines as a factor enabling more medicines to find their way onto the market sooner, hence increasing the market's access to these. One respondent in this cluster mentioned that review timelines for essential medicines will decrease if regulators gain confidence in review practices and trust the work and experience of other reviewers in other regions. The respondents in the neutral cluster mentioned that increased access is a function of affordability. Increased access will therefore only improve if governments take part in procuring the released medicines, otherwise private-sector suppliers will constrain the public's access to these medicines due to pricing issues. Another point that came across was that harmonisation will not help with the distribution – infrastructure and political will is needed to ensure access to essential medicines. There are many other cogs that need to work together with harmonisation to increase access to much needed essential medicines in SADC. The lack of political will is cited in literature as a

major barrier to harmonisation in SADC (Calder, 2016). The small disagreeing cluster did not give any open-ended justifications as to why they believe that harmonisation will not increase access to essential medicines in SADC.

4.6.3 Perceptions of whether ZaZiBoNa will increase Efficiency in the Workplace

Among the responses to this statement, 66.7% respondents (56.3% "Agree" and 10.4% "Strongly agree") were of the opinion that medicines registration harmonisation initiatives such as the ZaZiBoNa collaborative initiative will increase their efficiency in the workplace. This is in comparison to 25% who were neutral to this view and 6.3% who disagreed with it. Like with the previous two statements, the majority of the respondents were mostly agreed on the benefits of ZaZiBoNa.

The open-ended views of the respondents were more or less similar to those in sections 4.6.1 and 4.6.2. Most believe that there will be an increase in efficiency in their workplace because of the previously discussed factors, such as the elimination of duplication and the removal of administrative burdens. The neutral cluster mostly maintained that they were not sure of the effects of ZaZiBoNa on work efficiency. The ZaZiBoNa registration process is limited to the registration of essential medicines (Luthuli & Robles, 2017). The participants who were not sure of the effects of ZaZiBoNa probably have not utilised this process to register essential medicines.

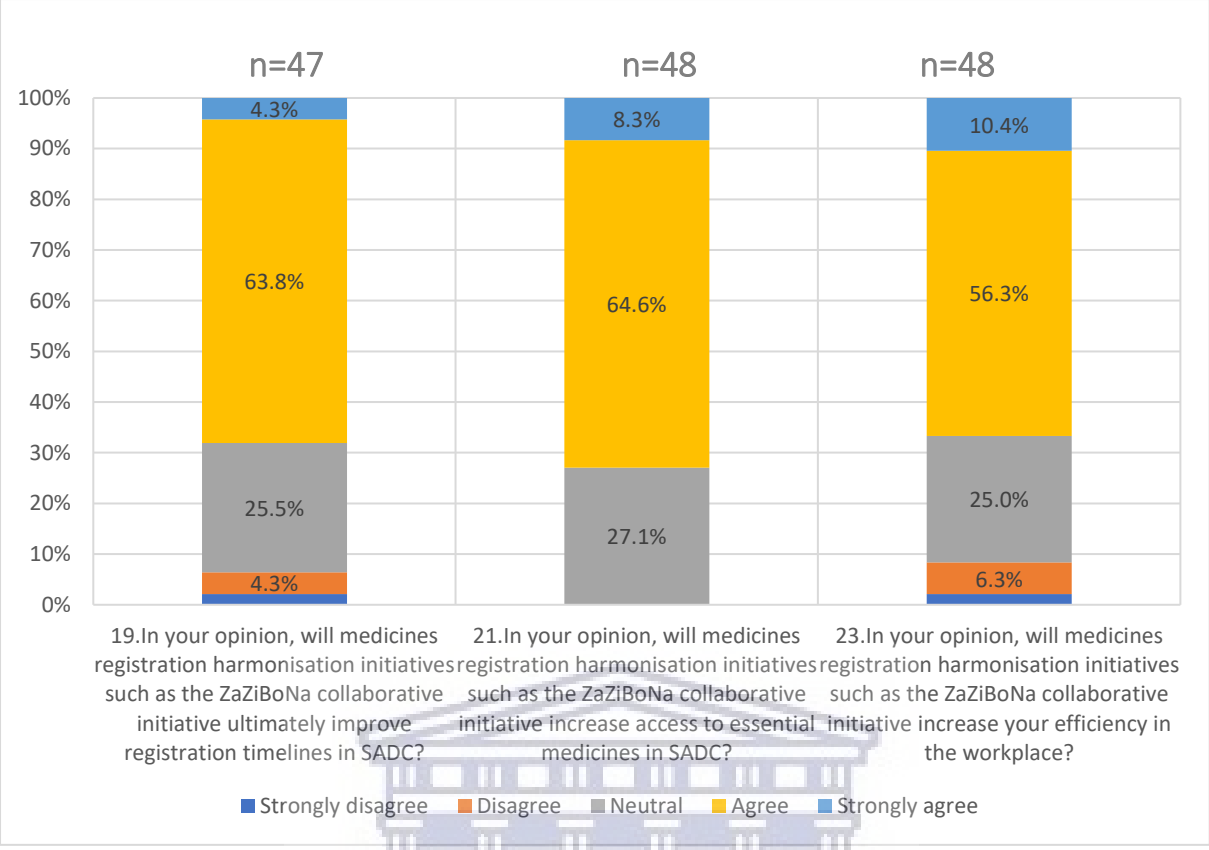

Figure 4.3: Respondents' Perceptions of the ZaZiBoNa Collaborative Initiative

4.6.4 Ease of accessing Information on ZaZiBoNa

Of the forty-three responses, 39.5% of the respondents specified that it is somewhat easy to access information on the ZaZiBoNa collaborative initiative, 34.9% (27,9% "Difficult" and 7% "Very difficult") found it difficult to access information on the initiative and 25.6% (20.9% "Easy" and 4.7% "Very easy") found it easy to access information related to the ZaZiBoNa collaborative initiative (Figure 4.4). The results point out that most found accessing the information not as smooth as expected, although it is not very difficult to access either. The primary sources of information on the initiative are industry associations, conferences, NMRA websites, the ZaZiBoNa website, colleagues, and the internet.

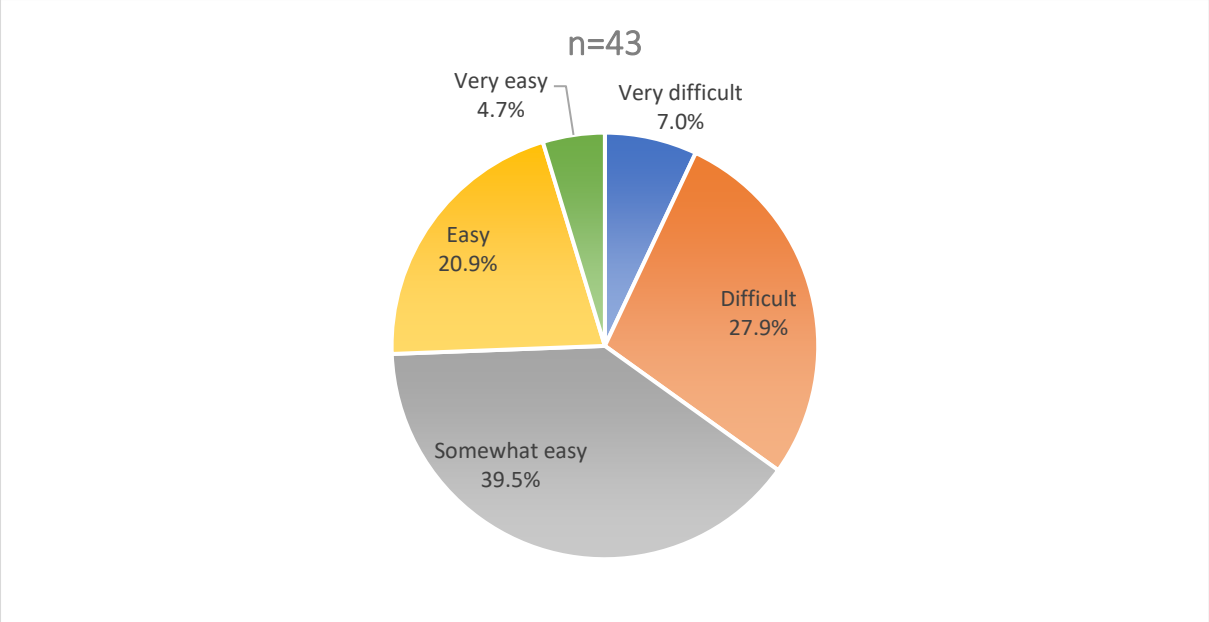

Figure 4.4: Respondents' Perceptions of the Ease of Accessing Information related to ZaZiBoNa

4.6.5 Perceptions on the Pace at which New Medicines are being registered in SADC

In total, forty-one valid responses were obtained for this question. The response for this question was that the perception on the pace at which medicines are being registered in SADC was slow (43.9%) to very slow (14.6%). Of the forty-one responses, 36.6% of respondents rated the registration process at an average speed and only 4.9% rated it as fast (Figure 4.5). No respondents rated the pace of medicines registration as very fast. These results show that the current pace at which new medicines are registered in SADC are viewed as undesirably slow to average. This can be attributed to the many problems that NMRAs face in SADC, such as a lack of the type of expertise required for regulatory assessments and financial resource constraints (Ndomondo-Sigonda *et al.*, 2018).

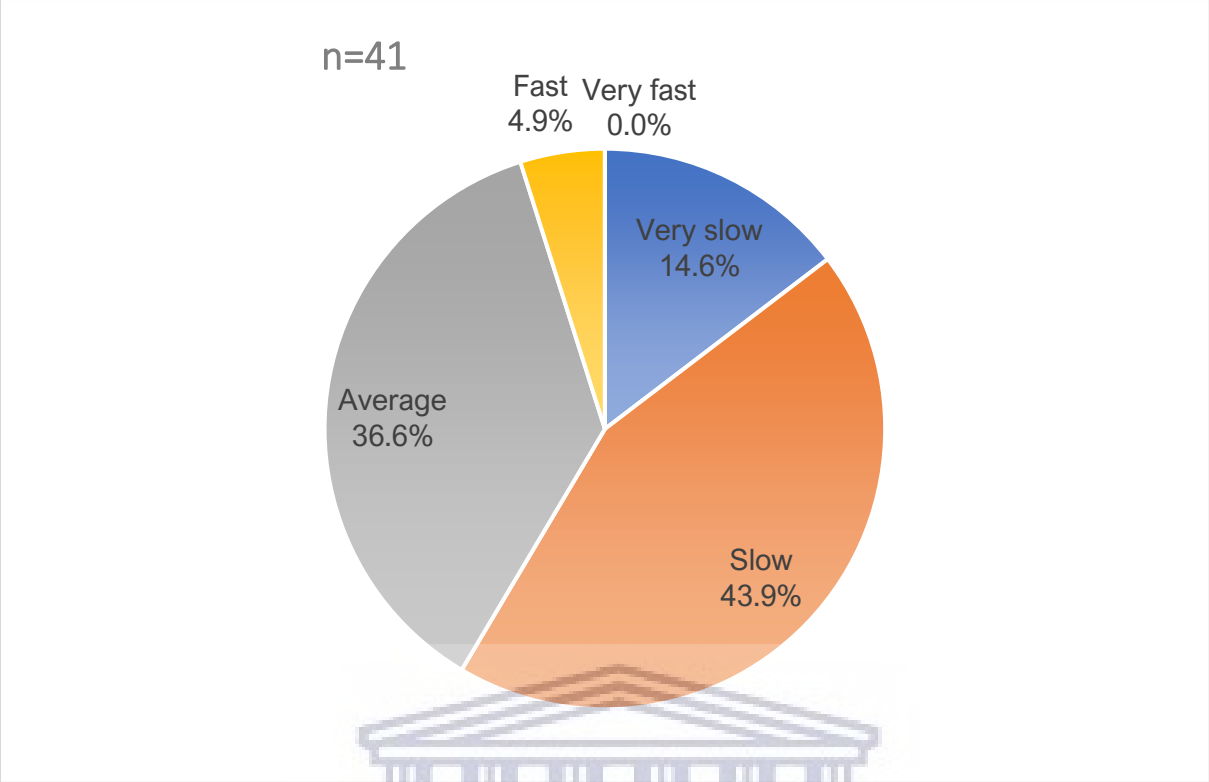

Figure 4.5: Respondents' Perceptions of the Pace at which New Medicines are being registered in SADC

4.6.6 Satisfaction with the Pace of Harmonisation and the Rate at which New Medicines are reaching the Market in SADC

Of the forty-seven responses to this question, 57.4% of respondents were dissatisfied (46.8% "Dissatisfied" and 10.6% "Very dissatisfied") with the rate at which new medicines are reaching SADC markets, while 38.3% were neutral to the same issue. Generally, there was more dissatisfaction on this issue, as only 4.3% of participants were satisfied with the rate at which new medicines reach SADC markets (Figure 4.6). Sithole *et al.* (2020) discussed factors that could hamper harmonisation, such as language barriers and countries' wishing to maintain their independence. Literature also revealed that different countries have different assessment criteria for medicine applications and there may be some bias in what is approved based on the need of the country's population (Calder, 2016). NMRAs are more likely to consider something

an essential medicine if it satisfies the important health care needs of the population in that country (WHO, 2021). The essential medicine will receive priority review over that of another medicine. This could be some of the factors that are affecting the rate at which new medicines are reaching the market in SADC.

There was a very similar response pattern among respondents with regards to the pace at which harmonisation activities are progressing in SADC. Most respondents (51.1%) were dissatisfied or strongly dissatisfied, while a considerable percentage (44.7%) remained neutral. Very few respondents (4.3%) recorded any satisfaction with the pace at which harmonisation activities are progressing in SADC with regard to new medicines registration. Literature has revealed that differences in economic development hamper harmonisation as some countries in SADC lack an effective NMRA, there is a great variation in policies and legislative frameworks, and some have a lack of expertise at NMRAs and limited financial resources (Kamwanja *et al.*, 2010). These barriers are affecting the pace at which harmonisation is progressing in SADC.

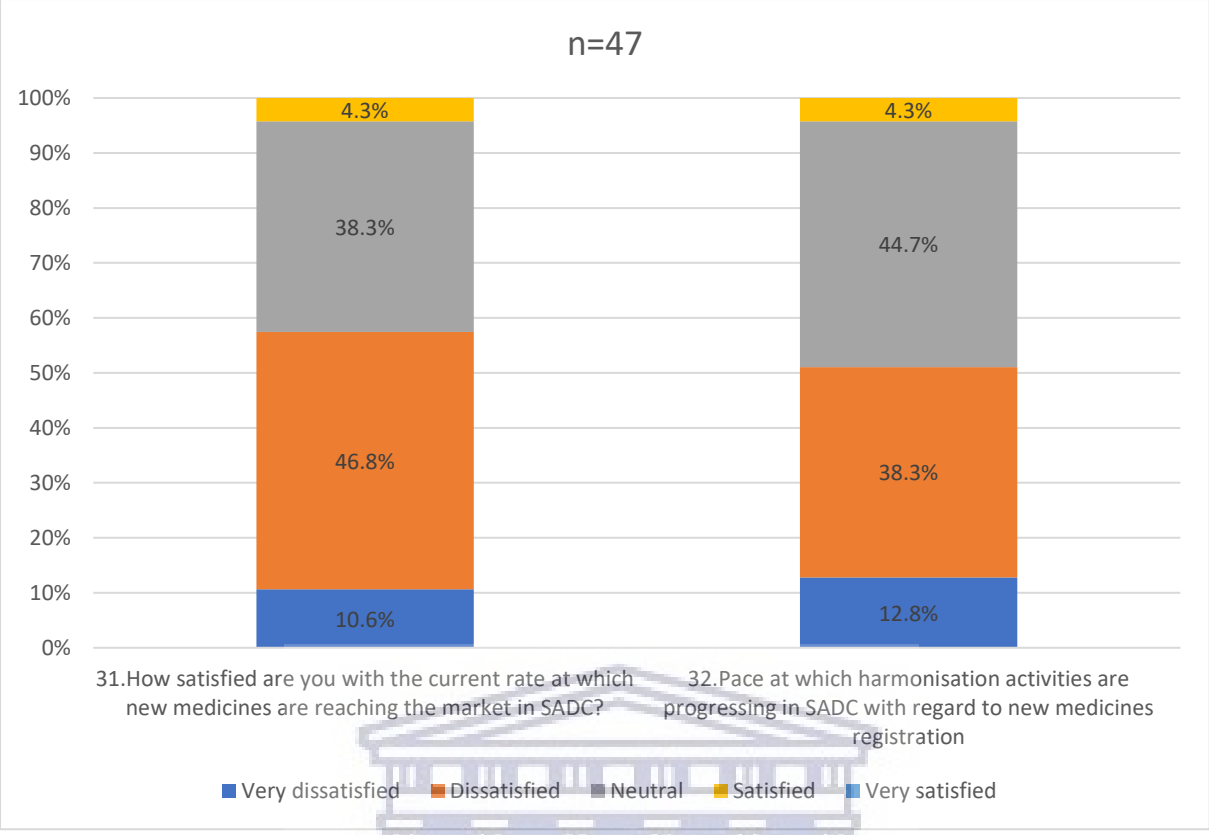

Figure 4.6: Respondents' Satisfaction with the Pace of Harmonisation and the Rate at which New Medicines are reaching the Market in SADC

4.7 ADVANTAGES OF HARMONISATION

The main advantages of harmonisation that were cited by the respondents were increased access to medicines, mutual recognition and collaboration, simpler work processes, reduced workload, shorter registration timelines, and more marketing opportunities. These advantages mentioned by respondents align with those that have been extensively discussed in literature (Azatyan, 2013; Ndomondo-Sigonda *et al*., 2018; Singh, 2015; WHO, 2008 & 2013). The most mentioned advantage was that harmonisation increases the efficiency of the registration process by simplifying processes and reducing workload. Twenty-two respondents subscribed to this view. Overall efficiency is increased as applicants can submit the same registration package to many markets without having to re-work the package. Respondents believe that efficiency is also increased at NMRAs as they could benefit from collaboration and work-sharing, thereby drastically reducing review timelines. They went on to explain that this

ultimately results in more medicines being registered, thereby resulting in greater access for consumers and more marketing opportunities for the pharmaceutical industry. The advantages listed are centred around the elimination of duplication which will result in increased efficiency and increased access to medicines. The respondents' answers were mainly centred around benefits for the pharmaceutical industry and regulators and neglected to mention more advantages for other stakeholders, such as consumers. Literature has discussed other advantages such as increased variety of medicines available on the market for consumers (WHO, 2014a) and improved public health as a result of good quality, safe, and effective medicines being available (Azatyan, 2013). Literature also revealed that drug development timelines would decrease (Valverde, 2015) and there would be a reduction in drug development cost (WHO, 2008), which could ultimately benefit the consumer. These advantages were not mentioned by any of the respondents. The advantages of harmonisation are listed as a theme in Figure 4.7 with various, related subthemes.

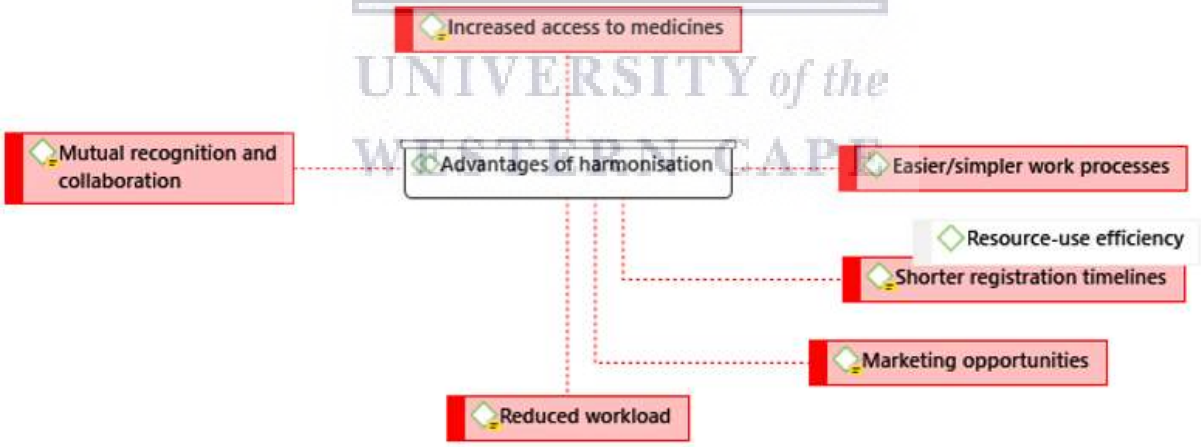

Figure 4.7: Respondents' Perceptions of Advantages of Harmonisation

4.8 DISADVANTAGES OF HARMONISATION

The most commonly outlined disadvantage mentioned by respondents was that harmonisation can come with coordination challenges that might reverse any benefits made by the elimination of duplication in evaluation and registration processes. Ten respondents discussed this disadvantage. Respondents went further to explain that each country wishes to operate independently, therefore making it difficult to reach alignment. Countries have different evaluation and registration regimes which can be difficult to align. The lack of technical expertise at NMRAs (WHO, 2014a) could be the cause of coordination challenges.

Even though the simplification of processes is an advantage, the result of this may be a loss of jobs, as mentioned by two respondents. Harmonisation could result in poor evaluation of medicines as there would be no full review of registration packages. A few participants mentioned that harmonisation can be more expensive for smaller pharmaceutical companies. Twelve respondents did not discuss any disadvantages that may arise as a result of harmonisation. Two respondents highlighted that the ZaZiBoNa collaborative initiative was limited to essential medicines – a limited scope. One respondent mentioned that the regulators at SADC NMRAs are inadequate in numbers, therefore leading to backlogs in the process. A study conducted in SADC mentioned the disadvantages of differing legislations and countries wanting to maintain their independence with regards to approval or rejection of an application (Sithole *et al*., 2020). These disadvantages were in line with respondents' views. However, a few new disadvantages of harmonisation were mentioned that had not been highlighted in the current literature, namely job losses, the process not being as beneficial to smaller companies, poor evaluation of medicines and limited scope of the ZaZiBoNa initiative. The disadvantages of harmonisation were listed as a theme with various, related subthemes, as shown in Figure 4.8.

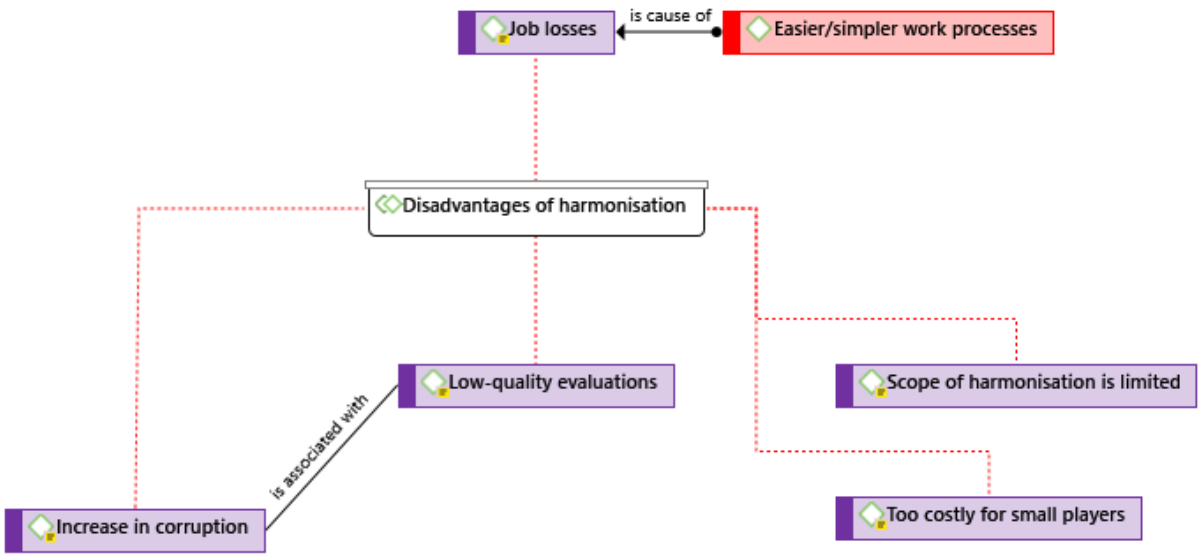

Figure 4.8: Respondents' Perceptions of Disadvantages of Harmonisation

4.9 BARRIERS TO HARMONISATION

The most discussed barrier by respondents was the fact that countries in SADC lack commitment to harmonise the evaluation and registration process. Each country wants its current regulations to be put ahead of others and this creates power tussles that derail the harmonisation process. Nine respondents held this view. The existence of wide differences in current regulatory regimes between countries were noted as another significant barrier to harmonisation. The respondents shared the view that for harmonisation to flow smoothly, countries involved need to have a common regulatory ground and this does not seem to be the case in SADC. The following three aspects were highlighted as barriers to harmonisation:

(i) the labelling requirements for each country are different,

(ii) the registration of medicines laws and regulations are different in each country, and

(iii) participating countries still reserve the right to accept or refuse a submission.

The respondents' arguments suggest that the existence of wide variances in regulatory regimes is one of the strongest barriers to harmonisation. This is exacerbated by the fact that some countries still need to develop regulatory regimes to be able to actively participate in harmonisation initiatives. Additionally, countries have the right to choose not to participate in harmonisation initiatives. Another barrier to harmonisation mentioned by respondents is lack of political will. Some respondents believe that the harmonisation process is mostly a political and government-to-government issue, more than a regulatory matter between regional regulatory bodies. Political will is needed to increase the pace of engagement and implementation and this will is generally lacking. One respondent believes that in addition to a lack of political will, there is negative political interference that results in a delayed pace of implementation of harmonisation initiatives. In the respondent's view, a lack of political will is strongly tied to the need to maintain sovereignty in the evaluation and registration of medicines. Five respondents labelled lack of trust between regulators from different countries as a barrier to harmonisation. This lack of trust results in an unwillingness to share information that could move the harmonisation process forward. Another three respondents mentioned a lack of adequate skills at various NMRAs as a barrier to harmonisation. Regulatory authorities, as it were, lack enough skilled manpower to coordinate the evaluation and registration of medicines under a harmonised regime. Closely related to skills is the issue of organisational capacity in implementing harmonisation regulations, strategies, and protocol. Respondents pointed to manpower shortages as a major capacity issue. NMRAs are currently struggling to cope with large work volumes and this results in low focus and less attention being given to harmonisation. Five respondents discussed how poor or a lack of communication and information-sharing was also a barrier to the harmonisation process. Lack of communication results in poor coordination of efforts and a lack of a common ground upon which regulatory processes could be harmonised. One respondent further mentioned language barriers,

especially with Mozambique and Angola being Portuguese-speaking countries with little regulation written in English. Four participants mentioned financial challenges as another barrier.

Quite a few barriers to harmonisation were listed by respondents. These barriers are in some instances the same or related to the barriers discussed in literature. The barriers mentioned by respondents could be the reason why they feel that harmonisation is not progressing at a fast-enough pace in SADC. Calder (2016) discusses the lack of political will and a lack of adequate relationships amongst SADC countries as barriers to harmonisation. Sithole *et al*. (2020) highlighted the barriers of countries wanting to maintain their independence, as well as some countries having different regulations, unique labelling requirements, and language barriers. The lack of skilled regulators, financial constraints, and variable interest in harmonisation are discussed in another paper detailing medicines registration harmonisation in SADC (Kamwanja *et al*., 2010). Azatyan (2013) highlighted the lack of communication as a barrier to harmonisation. Respondents did not mention any new barriers to harmonisation not listed in literature. Barriers to harmonisation were listed as a theme with various, related subthemes, as shown in Figure 4.9.

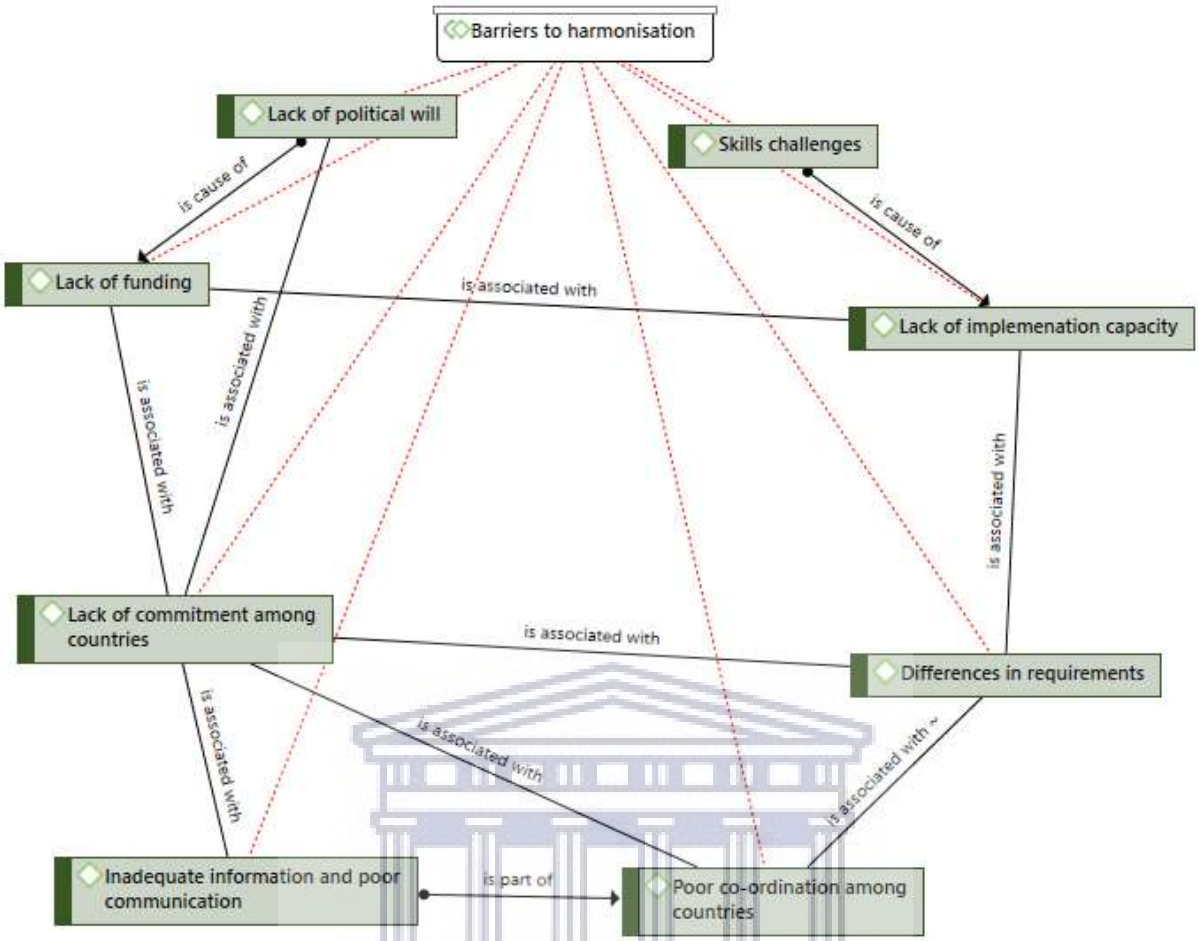

Figure 4.9: Respondents' Perceptions of Barriers to Harmonisation

4.10 PACE OF HARMONISATION IN SADC

Figure 4.10 highlights the relationship between the pace of harmonisation and the advantages, disadvantages, and barriers. The pace of harmonisation is negatively affected by existing or perceived barriers that are also associated with what are thought to be the disadvantages of the process. The realisation of harmonisation benefits is also affected by the barriers to the process. The advantages, disadvantages, and barriers are important for any NMRA or government to note prior to adopting harmonised guidelines. The advantages will highlight what the country can gain from harmonisation and the perceived barriers or disadvantages are useful to see

where further improvements can be made in the process. It is also useful for countries that have already adopted harmonisation to see how to improve the process in their own country.

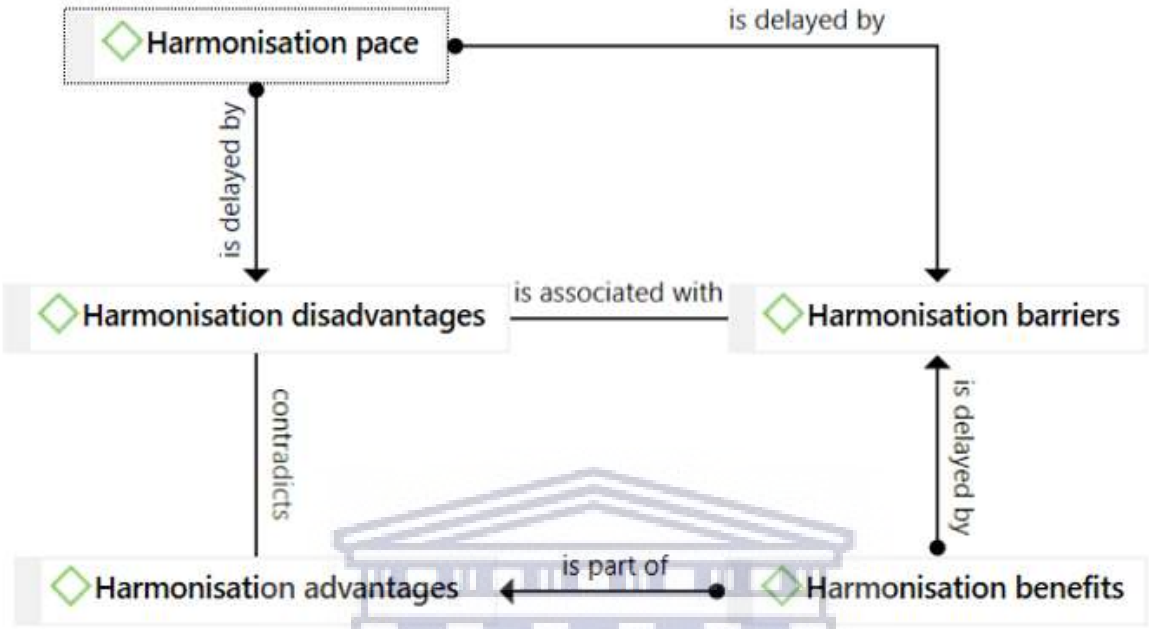

Figure 4.10: Relationship between the Pace of Harmonisation and the Advantages, Disadvantages, and Barriers

4.11 CHALLENGES OF COLLECTING AND ANALYSING DATA

There were a few challenges during the collection and analysis of the data. During the collection process, the researcher was allowed to communicate with only one SAHPRA representative. There was no way of tracking how many SAHPRA regulators had actually received the survey invitation. There was also no way of confirming that the reminders to complete the survey were sent out to the regulators to remind them. The survey invitation was sent to senior managers for them to disseminate to their teams.

Once the survey was closed, the data was extracted from Survey Monkey and analysed. There were originally eighty-eight responses. However, after going through the data extraction

document, there were only forty-nine responses left that could be utilised. The other participants had neglected to answer the open-ended questions or had only answered the demographic section.

4.12 STUDY LIMITATIONS

This study was conducted during the worldwide COVID-19 pandemic. It was therefore not possible to conduct in-person interviews with the participants from the pharmaceutical industry or regulators. Face-to-face interviews would have generated more meaningful data as open-ended questions could have been investigated further to obtain clarity. During the COVID-19 pandemic, SAHPRA was overwhelmed with submissions related to this pandemic and this could be a reason why none of the regulators took part in this study. The researcher had no way of following up with each regulator at SAHPRA as the survey was distributed through a central contact person at SAHPRA. This could have played a role in the zero-response rate from regulators. This study could have generated more responses if it were to be conducted over a longer period of time and with face-to-face or telephonic interviews. The respondents for this study were limited to those living and working in South Africa. It also only considered the perceptions of RAPs and regulators. There is a risk that the study may have response bias because of the small sample size. The newly adopted SAHPRA guidelines and harmonisation initiatives are still new to the industry hence many respondents were neutral to certain questions. Timelines for reviews have not yet been established hence respondents lack confidence in SAHPRA's implementation capabilities. In a few years industry would be able to give more accurate responses based on actual review timelines and ways of working. The study did not consider that the delay in registration approval could have been caused as a result

of factors outside the control of the NMRA such as poor-quality submissions from the regulatory industry.

CHAPTER 5
CONCLUSION AND RECOMMENDATIONS

5.1 CONCLUSION

This study identified whether the pharmaceutical industry (mostly RAPs) perceived that harmonisation initiatives that have been adopted in South Africa and SADC have improved efficiency in the workplace, improved timelines of medicines registration at NMRAs, benefited major stakeholders, and increased access to essential medicines. This study also gauged the study sample's perceptions of the advantages and disadvantages of and barriers to harmonisation, as well as how satisfied these representatives of the industry (mostly RAPs) are with the pace at which new medicines are being registered, at which harmonisation initiatives are progressing, and at which new medicines are reaching the market in SADC.

In all the questions relating to efficiency, only a few study participants believed strongly that the harmonised SAHPRA guidelines will increase various efficiencies. There was a common pattern where respondents were most likely to believe that the harmonised SAHPRA guidelines will improve various efficiencies or were neutral to it. More than half of the respondents believe that harmonisation will increase efficiency in their workplace. Harmonisation has shown to reduce duplication in many areas, optimise processes, and simplify processes in certain instances. The pharmaceutical industry highlights that there is evidence of improved efficiency at SAHPRA as a result of harmonisation. The participants who remained neutral on this topic report that harmonisation will not affect efficiency unless stakeholders, such as regulators, have the correct attitude toward harmonisation. The relatively small percentage of RAPs who believe that efficiency will not improve say that the new harmonised guidelines are rather hard to access and increase workload. A large percentage of the respondents believe that harmonisation will ultimately increase efficiency in the pharmaceutical industry, as well as at SAHPRA as evidenced by faster registration approvals.

More than half of the respondents believe that the new harmonised guidelines will improve the registration of essential medicines by shortening review timelines, thereby increasing access. The pharmaceutical industry professionals who were neutral to this view say they lack confidence in SAHPRA's capabilities. There was no consensus reached on whether the newly adopted harmonised guidelines would actually improve the registration approval timelines of NCEs. The RAPs again mentioned that they lack confidence in SAHPRA and its implementation capabilities and evaluation expertise for NCEs. More than half of the sample believe that there will be a definite improvement in the registration of generic medicines as a result of more efficient processes. It was, however, highlighted that these industry representatives lack confidence in SAHPRA utilising harmonisation effectively to promote faster registrations.

The representatives of the pharmaceutical industry strongly share the sentiment that the newly adopted guidelines will have a positive impact on the consumer as a result of increased access to medicines, greater variety, and to some extent lower prices for generic medicines. There is a common perception among RAPs that the benefits of the new harmonised guidelines will extend to regulators, with a few cautionary remarks that these benefits could be little or conditional, all dependant on the regulators. Overall, the sample shares the sentiment that the pharmaceutical industry at large is going to benefit from these changes in various ways, e.g. from faster registration approvals, decreased workload, increased sales, and increased investment in the pharmaceutical market by external investors. The RAPs expressed a few reservations that the benefits will be dependent on how harmonisation initiatives will be managed by SAHPRA.

The majority of the participants perceive the ZaZiBoNa collaborative initiative as having the ability to improve registration timelines in SADC. A minority shared a different view based on

their own understanding of what ZaZiBoNa entailed. A popular view among the RAPs is that the medicines registration harmonisation initiatives such as the ZaZiBoNa collaborative initiative will increase access to essential medicines in SADC, although there are concerns that other factors outside of harmonisation also affect this level of access. The majority of the respondents believe that ZaZiBoNa will increase their efficiency in the workplace as a result of a reduction in duplication of efforts and a reduced administrative burden as one registration dossier can be submitted to all the countries that have adopted ZaZiBoNa. RAPs who believe ZaZiBoNa will neither improve nor worsen their efficiency in the workplace maintain that they are not sure of the exact effects of ZaZiBoNa for efficiency. Most of the respondents highlight that it is not as easy as expected to find information on ZaZiBoNa, which may have contributed to their perceptions regarding efficiency.

The pace at which new medicines are registered in SADC is regarded as an average to slow process. Respondents are not satisfied with the rate at which new medicines are reaching the market in SADC. Results of the study also revealed that respondents are neither satisfied with nor neutral on the pace at which harmonisation activities are progressing in SADC with only a minority reporting any satisfaction on this matter.

This study has also highlighted the major perceived advantages and disadvantages of and barriers to harmonisation. Simpler work processes, reduced workload, and mutual recognition between or collaboration with international stakeholders has resulted in increased efficiency. The speeding up of review timelines as a result of these efficiencies has increased access to medicines and increased marketing opportunities for the pharmaceutical industry. These were singled out as some of the main advantages of harmonisation.

The representatives of the pharmaceutical industry highlighted four major disadvantages during this study:

- The reduction in workload and simplification of processes may result in job losses.
- Coordination challenges mean that many countries are at different levels of harmonisation.
- There may be poor evaluation of medicines as evaluations will now rely on RRA approvals instead of regulators performing a full review of the medicine dossier.
- Harmonisation may also be very costly for smaller pharmaceutical companies as they are unable to reap all the benefits.

This study revealed that there are numerous barriers to harmonisation. Many countries are not actively or willingly able to commit to the process as they still want to maintain their independence with unique regulations. These differences between countries makes it difficult to implement harmonisation. There is also a lack of political will from many countries. The other barriers that were mentioned was a lack of trust amongst countries, lack of skilled regulators to carry out reviews, lack of communication and financial restraints.

The study was aimed at both the pharmaceutical industry and regulators however unfortunately there were no responses received from regulators. The aims of the study were partially achieved due the zero-response rate from regulators however the data generated from this study did produce meaningful results. There was a definite agreement from industry that harmonisation initiatives that were adopted in South Africa and SADC have helped to increase efficiency in the work place. The study sample perceived that the increase in efficiency has also positively affected NMRAs thereby reducing approval timelines of essential medicines and generics thereby increasing access to these. It can be concluded that the study sample perceived that the positive effects of harmonisation may benefit to all major stakeholders such as regulators, the

pharmaceutical industry and the public as a result of increased efficiencies. There was no definite agreement that harmonisation would decrease registration timelines for NCEs. The participants of the study are not satisfied with the pace at which harmonisation is progressing in SADC or the rate at which new medicines are reaching the market in SADC. This is further evidenced by them rating the pace at which new medicines are registered in SADC as a slow to average pace. This study brought to light many advantages, disadvantages and barriers to harmonisation which may ultimately affect the pace at which harmonisation is progressing at.

5.2 RECOMMENDATIONS

Future researchers should consider face to face interviews with the pharmaceutical industry to gain more insight into their experiences with harmonisation. This will really help to gain additional insight as opposed to trying to interpret thought processes from answers on a survey. Telephonic interviews should also be considered for regulators in future with a more summarised questionnaire. The telephonic interviews will almost guarantee responses and the summarised questionnaire will encourage participation and engagement.

A study similar to the one that has been conducted could be conducted in the future to gain further clarity on the effect of harmonisation on the pharmaceutical industry and regulators. There may also be greater scope for industry to submit registrations via ZaZiBoNa thereby also gaining more experience on this collaborative initiative. Industry may become more knowledgeable on this initiative and be able to provide more realistic feedback based on actual experiences.

Future studies could also gain additional insights from other stakeholders such as consumers and healthcare professionals on how harmonisation has affected medicines availability,

innovation and supply. Future studies could be broadened to include perceptions on other harmonisation initiatives in Africa such as those in the EAC and ECOWAS regions.

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APPENDIX A

RESEARCH QUESTIONNAIRE

CERTIFICATE OF CONSENT

1. Please select your choice below.

By clicking on the "Agree" button below it indicates that:

• you have read and understood the above information

• you voluntarily agree to participate in the survey

• you are at least 18 years of age

If you do not wish to participate in the research study, please decline participation by clicking on the "Disagree" button.

Agree	Disagree

(Question 1a will only appear if the participant declines to participate in the study.)

1a. Why have you declined to participate in this study?

2. Which role best describes your current position?

Medicines Regulatory Authority Regulator	Regulatory Affairs Professional in the pharmaceutical industry	Other

Other (please specify):

Part A: South African Harmonisation Initiatives

3. Are you aware that the Medicines and Related Substances Act 101 of 1965 has been amended to make provision for harmonisation initiatives in South Africa?

Yes	No

4. Are you aware that the South African Health Products Regulatory Authority (SAHPRA) has recently adopted harmonised guidelines for certain regulatory activities?

Yes	No

(If the participant answers "No" to Question 3 then they will be redirected to Part B)

5. The newly adopted harmonised SAHPRA guidelines will likely result in increased efficiency in your current line of work?

Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

6. Please provide a reason for your answer

7. The newly adopted harmonised SAHPRA guidelines will likely result in faster registration approvals of essential medicines?

Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

8. Please provide a reason for your answer

9. The newly adopted harmonised SAHPRA guidelines will result in faster registration approvals of new chemical entities?

Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

10. Please provide a reason for your answer

11. The newly adopted harmonised SAHPRA guidelines will result in faster registration approvals of generic medicines?

Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

12. Please provide a reason for your answer

13. The newly adopted harmonised SAHPRA guidelines will ultimately benefit the public?

Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

14. Please provide a reason for your answer

15. The newly adopted harmonised SAHPRA guidelines will benefit regulators?

Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

16. Please provide a reason for your answer

17. The newly adopted harmonised SAHPRA guidelines will benefit the pharmaceutical industry?

Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

18. Please provide a reason for your answer

Part B: Southern African Development Community (SADC) Harmonisation Initiative

ZaZiBoNa is a collaborative medicines registration initiative in SADC. This initiative was formed to address problems such as backlog of product registrations, lengthy approval timelines for medicines and limited technical capacity at national medicines regulatory authorities in SADC. Please refer to www.zazibona.com for more information on this initiative.

19. In your opinion, will medicines registration harmonisation initiatives such as the ZaZiBoNa collaborative initiative ultimately improve registration timelines in SADC?

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

20. Please provide a reason for your answer

21. In your opinion, will medicines registration harmonisation initiatives such as the ZaZiBoNa collaborative initiative increase access to essential medicines in SADC?

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

22. Please provide a reason for your answer

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23. In your opinion, will medicines registration harmonisation initiatives such as the ZaZiBoNa collaborative initiative increase your efficiency in the workplace?

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

24. Please provide a reason for your answer

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25. How easy is it to find information relating to the ZaZiBoNa collaborative initiative?

Very difficult	Difficult	Somewhat easy	Easy	Very easy

26. What is your primary source of information for the ZaZiBoNa collaborative initiative?

27. In your opinion what are some of the advantages of harmonisation of medicines registration procedures in SADC?

28. In your opinion what are some of the disadvantages of harmonisation of medicines registration procedures in SADC?

29. In your opinion what barriers exist to the harmonisation of medicines registration procedures in SADC?

30. How would you rate the pace at which new medicines (NCEs & generics) are being registered in SADC?

Very slow	Slow	Average	Fast	Very Fast

31. How satisfied are you with the current rate at which new medicines are reaching the market in SADC?

Very Dissatisfied	Dissatisfied	Neutral	Satisfied	Very Satisfied

32. How satisfied are you with the pace at which harmonisation activities are progressing in SADC with regard to new medicines registration?

Very Dissatisfied	Dissatisfied	Neutral	Satisfied	Very Satisfied

APPENDIX B

HUMANITIES AND SOCIAL SCIENCE RESEARCH ETHICS COMMITTEE APPROVAL

UNIVERSITY of the WESTERN CAPE

60 YEARS of hope, action & knowledge

22 April 2020

Mrs K Dhanraj
School of Pharmacy
Faculty of Natural Sciences

Ethics Reference Number: HS20/2/10

Project Title: Perceptions of the pharmaceutical industry and regulators in South Africa towards African Registration Harmonisation in Southern African Development Community (SADC).

Approval Period: 21 April 2020 – 21 April 2023

I hereby certify that the Humanities and Social Science Research Ethics Committee of the University of the Western Cape approved the methodology and ethics of the above mentioned research project.

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

Please remember to submit an annual progress report by 30 November each year for the duration of the project.

The Committee must be informed of any serious adverse event and/or termination of the study.

Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

Director: Research Development
University of the Western Cape
Private Bag X 17
Bellville 7535
Republic of South Africa
Tel: +27 21 959 4111
Email: research-ethics@uwc.ac.za

NHREC Registration Number: HSSREC-130416-049

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