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The Implementation of the African Union Model Law on Medical Products Regulation and the Establishment of the African Medicines Agency

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DECLARATION

I declare that *The Implementation of the African Union Model Law on Medical Products Regulation and the Establishment of the African Medicines Agency* is my own work, that it has not been submitted for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

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Date: 10 November 2022.

Signed: 

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LIST OF ABBREVIATIONS

AMA	African Medicines Agency;
AMRH	African Medicines Regulatory Harmonisation;
AMRH-PP	African Medicines Regulatory Harmonisation Partnership Platform;
API	Active Pharmaceutical Ingredient;
APIMF	Active Pharmaceutical Ingredient Master File;
AU	African Union;
AUDA-NEPAD	African Union Development Agency – New Partnership for Africa's Development;
CEN-SAD	Community of Sahel-Saharan States;
CHMP	EMA Committee for Medicinal Products for Human Use;
COMESA	Common Market for Eastern and Southern Africa;
CRO	Contract research organisation;
CRP	Collaborative Regulatory Procedures;
DRC	Democratic Republic of Congo;
EAC	East African Community;
ECCAS	Economic Community of Central African States;
ECOWAS	Economic Community of West African States;
EDCTP	European and Developing Countries Clinical Trials Partnership;
EMA	European Medicines Agency;
EPAR	European Public Assessment Report;
EPI	Expanded Program on Immunization;
EU	European Union;
FDA	Food and Drug Administration;
FPP	Finished pharmaceutical product;
GBT	Global Benchmarking Tool;

GMP	Good Manufacturing Practice;
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use;
IGAD	Intergovernmental Authority on Development;
IMS	Information Management System;
IPR	Intellectual Property Rights;
LMIC	Low- and middle-income country;
LoQ	List of questions;
MA	Marketing Authorisation;
MAGHP	Swissmedic procedure for Marketing Authorisation for Global Health Products;
MCAZ	Medicines Control Authority of Zimbabwe;
MRH	Medicines Regulatory Harmonisation;
NAFDAC	National Agency for Food and Drug Administration and Control;
NCE	New Chemical Entity;
NDA	National Drug Authority (of Uganda);
NEPAD	New Partnership for Africa's Development;
NMRA	National Medicines Regulatory Authority;
NWU	North West University;
OCEAC	Organization of Coordination for the Fight Against Endemic Diseases in Central Africa;
PDCO	EMA Paediatric Committee;
PEPFAR	U.S. President's Emergency Plan for AIDS Relief;
PIL	Patient information leaflet;
PMPA	Pharmaceutical Manufacturing Plan for Africa;
PPB	Pharmacy and Poisons Board;
PRAC	EMA Pharmacovigilance Risk Assessment Committee;
QCL	Quality control laboratory;

QMS	Quality Management System;
RCORE	Regional Centre of Regulatory Excellence;
REC	Regional Economic Community;
RTO	Regional Technical Officer;
SADC	Southern African Development Community;
SDC	Swiss Development Cooperation Agency;
SF	Substandard and Falsified;
SmPC	Summary of product characteristics;
SRA	Stringent regulatory authority;
SRP	Stringent review procedure;
SSA	Sub-Saharan Africa;
TMDA	Tanzania Medicines and Medical Devices Authority;
TRIPS	Trade-Related Aspects of Intellectual Property Rights;
TWG	Technical Working Group;
UMA	Arab Maghreb Union;
UN	United Nations;
USFDA	U.S. Food and Drug Administration;
WHO	World Health Organization;
WHO-PQP	World Health Organization Prequalification Program.

DEDICATION

To O'glady and Mark,

Thank you for all your support and sacrifices.

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ABSTRACT

Within Africa, there is insufficient access to quality, safe, efficacious and affordable medical products which can partly be attributed to lack of robust regulatory systems, a lack of competent regulatory professionals in national medicines regulatory authorities (NMRAs) and ineffective regional collaborations among NMRAs. In response to national regulatory challenges, a number of regional harmonisation efforts were introduced through the African Medicines Regulatory Harmonisation (AMRH) initiative to, among others, expedite market authorisation of medical products and to facilitate the alignment of national legislative frameworks with the African Union (AU) Model Law on Medical Products Regulation. The goals of the model law include to increase collaboration across countries and to facilitate the overall regional harmonisation process. The AMRH initiative is proposed to serve as the foundation for the establishment of the African Medicines Agency (AMA). The AMA will, as one of its mandates, coordinate the regional harmonisation systems that are enabled by AU Model Law implementation. However, AU Model Law implementation targets have not been fully met, and several countries are yet to ratify the AMA treaty.

This study aimed to: (i) analyse the rationale, perceived benefits, enabling factors and challenges of domesticating the AU Model Law by African countries and of the establishment of the AMA and to (ii) examine the agenda-setting process leading to AMA treaty ratification, using the five countries that had ratified by September 2020 as case studies.

A qualitative approach was employed in this study. Firstly, a census survey involving African countries and all Heads of NMRAs and a nominated senior competent person was employed. Damschroder's Consolidated Framework for Implementation Research served as the conceptual and analytical framework for gaining a comprehensive understanding of model law implementation. Semi-structured key informant interviews were then conducted with NMRA and

Ministry of Health staff from the five countries. Kingdon's Multiple Streams Framework was used to frame the empirical results in a theoretical context.

This study found that the enabling factors for these initiatives are the desire to have harmonised regulatory systems in Africa that allow for collaboration, the presence of strong political will and leadership, the presence of advocates for the initiatives, advocacy from NMRAs, and the availability of financial and human resources. The challenges reported included, *inter alia*, lack of the mentioned enabling factors, competing priorities at the national level and lengthy administrative and legislative procedures. In terms of the agenda-setting process leading to treaty ratification, African countries face several regulatory challenges that all served as motivators for the AMA's establishment. The separate problem, policy and politics streams then came together which allowed the AMA treaty to make it onto the governmental agenda. Policy entrepreneurs were responsible for the coupling of the streams and windows of opportunity for treaty ratification consequently emerged in Ghana and Rwanda.

Overall, Africa's existing regulatory challenges justified model law implementation and the AMA's establishment. These initiatives, which were perceived to harmonise regulatory systems and improve medical products access, were enabled by NMRA staff despite challenges such as competing priorities and lack of political will.

CHAPTER 1

INTRODUCTION

1.1 Introduction

This chapter introduces the research study. First, the study background is described, including the challenges faced by healthcare systems in Africa related to access to medical products. Among other factors, the challenges have been attributed to weak or absent medicines regulatory systems. The medicines regulatory harmonisation initiatives that are being implemented on the continent to address these challenges are also discussed. In addition, the rationale for conducting this research is discussed. The research questions, study aim and specific objectives are then presented. An outline of the thesis is also provided.

1.2 Background

1.2.1 Regulatory systems and maturity level in Africa

There are 55 countries in Africa and a population of approximately 1.2 billion people making it the second most populous continent in the world (1–3). There is also a high burden of communicable and non-communicable diseases on the continent which presents considerable challenges for the healthcare system (1). For example, Africa is home to 11% of the world's population yet it contends with 60-75% of the world's HIV/AIDS cases and over 90% of the annual global malaria cases (4,5). In addition, Africa has for decades faced the challenge of insufficient access to quality-assured, safe, efficacious and affordable medical products which poses a significant challenge to public health (6,7). Access to medical products for non-communicable diseases is also becoming equally important as these conditions are predicted to become the leading cause of death on the continent by 2030 (3,5,8). However, there are delays of 4-7 years between first regulatory submission of product dossiers to a well-resourced National Medicines Regulatory Authority (NMRA) and final approval in sub-Saharan Africa (5,9,10). Pharmaceutical companies have therefore declined to supply medical products to certain African markets and they have cited these lengthy registration times as one of the reasons (9). Reports have also stated that 10% of medicine samples in sub-Saharan Africa are substandard or falsified, and these

samples include lifesaving products such as antimalarials, antibiotics and antiretrovirals (11). 'Substandard' medical products are those which are authorised but fail to meet their quality standards or specifications whereas 'falsified' medical products refers to those that deliberately/fraudulently misrepresent their identity, composition or source (12). These challenges have partly been attributed to weak or absent medicines regulatory systems (6,13), which include unclear policies, as well as incomplete or incoherent legal and regulatory frameworks. Furthermore, there are challenges such as high staff turnover and lack of competent regulatory professionals in NMRAs, as well as poor regulatory infrastructure and ineffective regional collaborations among NMRAs (3,6–8,10,13–22). For the effective regulation of medical products to occur, there is a need to have a comprehensive legal basis with appropriate and adequate governance mechanisms, robust technical expertise and scientific tools, sustainable financing, regulatory activity coordination, and performance assessments through continuous monitoring and evaluation (9).

In most countries, pharmaceutical oversight is a function of medicines and allied substances control regulations which relate to the control and regulation of a number of elements of the pharmaceutical value chain, ranging from the registration of medical products to how patients access these products (8). These regulations also outline the functional and operational structures of NMRAs as well as define their roles and responsibilities, and funding and reporting structures (8). NMRAs are crucial government institutions that are mandated to regulate medical products and ensure that products in the country are quality-assured, safe and efficacious. NMRAs also enforce regulatory functions in the discharge of their day to day duties; they combat the circulation of substandard and falsified medical products and regulate the manufacture of medical products, clinical trials, and the marketing of medical products (6,7,9,13–15,18,23–26).

The 'maturity level' concept is incorporated in the Global Benchmarking Tool (GBT) used by the World Health Organization (WHO) to objectively evaluate regulatory systems (27). The GBT allows WHO and NMRAs to assess the overall maturity of a regulatory system on a scale of 1 (the existence of some regulatory

system elements) to 4 (operation is at an advanced level of performance and there is continuous improvement) (27). Africa has no NMRA operating at maturity level 4. However, the NMRAs of Tanzania, Ghana, Egypt, Nigeria, and South Africa operate at maturity level 3. Tanzania, Ghana, and Nigeria have maturity level 3 status for medicines and imported vaccines whereas Egypt and South Africa's maturity level 3 status is for vaccines regulation (locally produced and imported) (28,29). The NMRAs of these five countries represent effective regulatory systems on the African continent. Other African NMRAs are currently being assessed (28,29). All NMRAs on the continent eventually report to either the Ministry of Health as the overall responsibility lies with the Minister of Health (9), or they report directly to the Executive. Additionally, many African countries lack harmonised technical requirements which impedes timely access to essential medical products (9,16,30,31). Regulatory harmonisation refers to the process of NMRAs aligning technical requirements for the development and marketing of medical products (32).

The pharmaceutical industry is increasingly becoming globalised and decentralised, and this has had an impact on regulatory issues everywhere (20). There is no single regulatory authority, partly due to the globalisation of the manufacturing of medical products, that can individually guarantee the safety of all medical products in its territory efficiently and effectively (3,25,33,34). In the present context of linked supply chains, one country is increasingly dependent on the quality and safety systems in place in another country (3,25), and a regulatory system that is weak in one country will inevitably have a considerable impact on another country (20). Currently, the problems that are created by the ineffective regulation of medical products transcend national borders and have global consequences (19). In addition, regulatory legislation is created at the national level and therefore neighbouring countries in a regional bloc can have significantly different procedures and systems for regulating medical products (6,14,15). When regulatory requirements are not harmonised, this results in NMRAs being under no obligation to adopt another country's regulatory decisions, even in cases where NMRAs receive identical evidence dossiers (6,15). Applicants and manufacturers will be legally required to submit

duplicative evidence dossiers and applications for marketing authorisation to a number of NMRAs where they intend to register their products (6,14,15,35). These dossier submissions have time and cost implications with resultant delays in patients accessing medical products (6,15). The absence of harmonised technical requirements between countries is one of the reasons for NMRA backlogs and the duplication of effort by NMRA staff (6,15).

1.2.2 The Benefits of Regulatory Harmonisation

While these challenges prevail, interventions that can positively and effectively improve health outcomes exist (36). For instance, regulatory harmonisation offers several benefits to the various pharmaceutical stakeholders, including patients and the pharmaceutical industry (17,34,37–39), and there are sound arguments for harmonisation from both a theoretical and a practical perspective (34). Harmonisation may enable African NMRAs to leverage international expertise, stay up to date with international best practices and standards, and operate efficiently in a resource constrained environment through information sharing and the recognition of decisions made by mature NMRAs (17,30,34,39). Additionally, the harmonisation and coordination of regulatory efforts on the continent is necessary to streamline pre-marketing authorisations, make the post marketing surveillance system more robust, create an enabling environment for local production, and improve timely access and delivery of medical products for patients who most need them (3,14). Harmonisation could also result in more streamlined communication systems between the AU Member States, encouraging the use of a common regulatory language, international best practices and adaptation to the globalisation of the pharmaceutical industry (20). Furthermore, the pharmaceutical industry benefits from harmonisation by potentially having access to new markets and high levels of compliance with regulatory requirements (17,30,39). In various aspects of health systems, the harmonisation of approaches is viewed as a successful method for public health improvement, not only in Africa but globally (13). Therefore, academics, policymakers and practitioners have invested in advancement efforts towards harmonised processes and systems (13).

1.2.3 The African Medicines Regulatory Harmonisation Initiative

To address the challenges that have been highlighted, a number of harmonisation initiatives have been developed in Africa such as the African Medicines Regulatory Harmonisation (AMRH) initiative, the African Union (AU) Model Law on Medical Products Regulation, and the yet to be established African Medicines Agency (AMA). The AMRH initiative was conceptualised in 2009 and it was motivated by the need to remove obstacles preventing access to medical products for patients in Africa (10). The AMRH initiative was then formalised in the same year (7,9,31,40), and aimed to improve the health of the population by creating effective, efficient and transparent regulatory mechanisms to achieve faster medical product approvals and ensure their subsequent availability, especially for the treatment of neglected and priority diseases in various African markets (9,18,26,31). The AMRH initiative was created with the intention of increasing access to medical products through effective harmonisation of regulatory requirements and practices. This harmonisation among African NMRAs would enable them to meet internationally acceptable regulatory standards. In addition, the initiative intended to support AU Member States and regional initiatives that sought to align medicines regulation, fill in challenges faced in medical products regulatory capacity, as well as promote local pharmaceutical production and trade across African countries (41–46). The AMRH initiative also aimed to improve Africa's fragmented medical product registration and regulatory system by transitioning from a country-focused approach to a simplified collaborative regional approach (9,10). Furthermore, the initiative intends to expand its scope of work gradually, commencing with generic medicine registration and moving towards oversight of vaccine clinical trials, pharmacovigilance, and the registration of new chemical entities, medical devices and diagnostics (9,10,16). In order for the scope of work to be successfully expanded, the different partners and stakeholders need improved coordination as well as harmonisation to avoid duplicative effort, fragmented priorities and ensure the optimal use of available resources (10). Moreover, the AMRH initiative, from a regulator's point of view, assists with functioning at an optimum level in a resource constrained environment (30). The AMRH initiative has

harmonised regulatory systems and successfully demonstrated the possibilities of coordinating regulatory harmonisation at a continental level (3).

The implementation of the AMRH initiative falls under the framework of the Pharmaceutical Manufacturing Plan for Africa (PMPA), which was endorsed in 2007 by the AU Conference of Ministers of Health in response to a call by the African Heads of State and Government in 2005 (5,9,13,16). In Africa, there have been ongoing regulatory harmonisation initiatives based on the decision of the AU Heads of State and Government on the PMPA and the AU Roadmap on Shared Responsibility and Global Solidarity for AIDS, Tuberculosis and Malaria Response in Africa, which gave the quality, safety, efficacy and affordability of medicines, including blood products, a high priority (3,47). The aim of the PMPA, which identified the creation of an enabling regulatory environment to be a priority that needs addressing, is to ensure that African countries are able to provide all their citizens with quality-assured, safe and efficacious essential medicines as part of their national obligations, in addition to the realisation of both direct and indirect economic growth (3,8,13,31,36,47–49). The objective of the PMPA, broadly speaking, is to improve the quality of medical products even in countries that are neither involved in local pharmaceutical production nor have a desire to be (8). Within the framework of the PMPA, the AMRH initiative has been implemented over the last ten years by the African Union Development Agency – New Partnership for Africa's Development (AUDA-NEPAD), in collaboration with WHO and partners, with the intention to support the strengthening of medical products regulatory systems in Regional Economic Communities (RECs) and AU Member States (3,13,16,21,47,50).

RECs cluster individual countries into sub-regions with the objective of attaining better economic integration and to coordinate the implementation of AUDA-NEPAD programmes (3,21). There are 8 RECs in Africa: Arab Maghreb Union (UMA); Common Market for Eastern and Southern Africa (COMESA); Community of Sahel-Saharan States (CEN-SAD); East African Community (EAC); Economic Community of Central African States (ECCAS); Economic Community of West African States (ECOWAS); Intergovernmental Authority on

Development (IGAD); and the Southern African Development Community (SADC) (51). Within the PMPA framework, the AMRH initiative has been implemented, in collaboration with WHO and partners, with the intention of supporting the strengthening of regulatory systems in these RECs and member states (3,13,16,21,47,50). The partnership has resulted in RECs and regional health organisations being supported to serve as regional information sharing platforms and benefitting from harmonised regulatory requirements, standards, systems, legislation and practices (3,21,26). The intention of the work done by RECs is to be a stepping stone for the harmonisation of activities in Africa (3). Under the AUDA-NEPAD, regional harmonisation activities started with the EAC as it was selected as the first region to begin the implementation of its medicines regulatory harmonisation plans (3,7,10,31,37,40). The EAC consists of Burundi, Kenya, Rwanda, South Sudan, Tanzania, and Uganda (5,7,11,52). The original thinking was to pilot the AMRH initiative in one REC, the EAC, for learning purposes and then have a gradual geographical expansion of the AMRH initiative until it covered all countries in Africa (9–11,53). The success of the EAC's regulatory harmonisation initiative is considered by some scholars to have an influence on the success of forthcoming initiatives, especially at a time when Africa is working towards an African Medicines Agency (7,20).

1.2.4 The African Union Model Law on Medical Products Regulation

Ndomondo-Sigonda and colleagues (9) believe that disparities in legal provisions of key regulatory functions in some African countries were potentially leading to delays in access to and availability of essential medical products and this calls for regulatory convergence towards a common framework. As a result, the AUDA-NEPAD and key stakeholders developed the AU Model Law on Medical Products Regulation, hereafter referred to as the AU Model Law. The aim of this non-prescriptive model legislation is to address the existing legislative gaps as well as to streamline regulatory systems and facilitate the overall regional harmonisation process (54,55). The development of the draft AU Model Law was done through the AMRH initiative platform and endorsed by the Pan African Parliament (PAP) Committee on Health, Labour and Social Affairs (13,53). Through the AU Model Law domestication process, a country can adapt the AU

Model Law so that it is consistent with its constitutional principles and legal system, as well as amend or repeal any inconsistent national laws (10,15,31,56). In countries that have inadequate legislation and regulatory frameworks, the process of domesticating and implementing the model law must be expedited to allow for the establishment of properly functioning NMRAs (53). The long term goal of the AMRH initiative is to establish the AMA, which will have the mandate of overseeing the registration of specific medical products and coordinating regional harmonisation systems in Africa (57). Therefore, the development of the AU Model Law is interpreted within the context of these overarching efforts towards regulatory harmonisation in Africa (14). These efforts in regulatory systems harmonisation are a pivotal aspect when laying the foundation for establishing the AMA (3,13,14,23,47,58).

1.2.5 The African Medicines Agency

The AU Executive Council Decision EX.CL/Dec.857 (XXVI) of January 2015 forms the basis for the establishment of the AMA and endorsed the milestones for establishing the Agency within the context of the AMRH initiative, which is a part of the implementation of the PMPA (10,40,50). The AMA's vision is to ensure that all Africans have access to affordable medical products, that meet internationally recognised standards of quality, safety and efficacy, for priority diseases/conditions (3,36,48,59,60). The AMA is intended to be an AU organ that is legally mandated by member states, and it aims to provide a platform for the coordination and strengthening of ongoing regulatory harmonisation initiatives across the continent (1,3,33,36,40,47,48). In addition, the AMA will be a specialised agency of the AU and it plans to ensure the optimal use of scarce resources by pooling expertise, capacities and strengthening existent networks. It also has the intention to offer guidance, in addition to complementing and enhancing the harmonisation efforts of RECs. This will potentially contribute to enhanced accessibility of quality, safe, efficacious and affordable medical products (1,3,33,36,40,47–49,60,61). Furthermore, AMA seeks to enable expedited approvals for medical products that meet the health needs of Africans, particularly for conditions that affect Africa disproportionately, while also fostering the competitiveness of locally manufactured medical products (3,49).

The AMA proposes to work collaboratively with NMRAs, provide technical guidance, reduce duplicative efforts, and ensure cost-effective use of limited resources (9,40,62). It is worth noting that AMA will not replace NMRAs or the sub-regional medicines regulatory authorities which will be established by RECs (3,10,50,60). Instead, the AMA aims to complement the efforts of NMRAs, RECs and ROs in the process of creating a conducive environment for the pharmaceutical industry to develop through enhanced coordination of the various stakeholders involved in African regulatory harmonisation initiatives (10). NMRAs will still assess the majority of medical products, have their decision making roles and put in place market controls for their specific territories (3,10). The AMA also intends to build on the experiences and strengths of the Regional Centres of Regulatory Excellence (RCORE) model in order to develop regulatory science specialists in Africa (57). An RCORE is an institution, or partnership of institutions, with specific expertise in regulatory science, proven capacity as well as capabilities in the training or delivery of services in at least one of the identified categories of regulatory and managerial functions (10,63). These institutions include, but are not limited to, NMRAs, academic institutions, scientific and research institutions, information dissemination centres, and pharmacovigilance centres (63). The criteria for establishing RCOREs was developed by the AMRH initiative, through the Continental Technical Working Group on Regulatory Capacity Development, as part of the initiative's mandate to develop and strengthen regulatory capacity in Africa (10,13). There is a desire for the AMA to create more RCOREs, and support them with curriculum development and training programmes so as to have more specialised and certified regulatory officers for AU Member States and RECs (40).

In the context of moving towards the establishment of the AMA, the AMA treaty must be signed and then ratified. Ratification refers to the national procedure where the AU Member State puts in place a law that allows for the implementation of the treaty (64). The AMA treaty is open to AU Member States for signature and ratification/accession and it entered into force thirty days after the deposition of the fifteenth instrument of ratification/accession (11,49,50,59–62). African health leaders are demonstrating their determination to rectify the

regulatory challenges faced in Africa and on 12 June 2019, the Republic of Rwanda became the first AU Member State to sign the treaty (1,58,59). Currently, the final form that the AMA will take is unclear (11). However, it has been decided that the AMRH initiative shall serve as the foundation for the establishment of the AMA (1,3,10,11,13,37,49,58). The AU, RECs and partners are also leveraging lessons learned from past experiences of harmonisation models and schemes around the globe, such as those in Europe, America and Asia, to assist Africa attain an efficient harmonisation process (37). Despite the challenges faced in regulatory harmonisation, the value of regulatory systems to global health must continue to be communicated, and the AMA can potentially overcome these harmonisation challenges as well as facilitate harmonisation by galvanising technical support, regulatory expertise and resources at a scale that neither the national nor regional initiatives can match (3). The AMA is therefore expected to become Africa's focus of regulatory standards harmonisation, process optimisation, and resource coordination across the continent (11). Moreover, the AMA is envisaged to represent a single, credible African voice that has more weight compared to having individual voices on regulatory issues on the continent (3).

1.3 Rationale for the Study

Conducting research on "The Implementation of the African Union Model Law on Medical Products Regulation and the Establishment of the African Medicines Agency" is important to a number of stakeholders, and for a number of reasons. From a regional and continental perspective, there are several interlinked, published policy frameworks, guidelines and strategies that relate to access to medical products and improving health in Africa. Promoting sustainable access to quality-assured, safe, efficacious and affordable medical products, and the integration of local pharmaceutical production into the overall health systems strengthening package are also critical priorities for African leaders (3,8,36,48).

The African Medicines Regulatory Harmonisation (AMRH) Strategic Framework (2016-2020), which was developed by AUDA-NEPAD, builds on previous harmonisation efforts and it is meant to offer ongoing support to AUDA-

NEPAD and its partners (37,65). Strategic Direction I is on policy alignment and regulatory reforms, and it has a strategic objective of enhancing policy coherence in RECs and AU Member States for public health and pharmaceutical industry development (65). Some of the targets relating to Strategic Direction I include having at least three regions adopting regional policies and legal frameworks for medical product regulation by 2020 (66), and at least 25 countries domesticating the AU Model Law by 2020 (10,14,66). Strategic Direction II has a specific objective of increasing the use of harmonised policies and regulatory frameworks by AU Member States (65). The increased use of harmonised policies and regulatory frameworks may contribute to faster, quality, predictable and transparent approval of medical products and health technologies. However, the implementation targets for the AU Model Law have not been fully met. Some of the reasons that have been cited to explain poor policy implementation in Africa include incoherent policies, the absence of enforcement and accountability mechanisms, and insufficient financial resources for policy implementation (66).

There are several countries that have adopted or adapted the AU Model Law and they include Burkina Faso, Burundi, Ivory Coast, Lesotho, Mozambique, Namibia, Rwanda, Seychelles, The Gambia, the Kingdom of Eswatini, United Republic of Tanzania (Zanzibar), and Zimbabwe (67,68). By studying these countries, lessons and best practices that can be emulated when revising national medicines regulatory systems using the AU Model Law as the reference document can be uncovered. Studying these countries will also potentially offer examples of domesticating and implementing a version of the AU Model Law that best responds to a country's respective needs in order to set up a streamlined regulatory system that ensures that medical products meet international standards of quality, safety and efficacy. For countries that are attempting to domesticate and implement the model law, lessons can be learned from the countries which report in this study that they have found the AU Model Law to be useful, and these lessons will potentially catalyse implementation in other African countries so that they too can reap the technical level benefits of the model law. In addition, research must be conducted on the perceived benefits (or lack thereof) of domesticating and implementing the model law, and the country level enabling

factors and challenges. There is a need to understand the current status of domestication and implementation of the AU Model Law in order to provide a foundation for identifying the existing gaps and opportunities for improving the regulation of medical products, public health protection and promotion, and pharmaceutical industry advancement on the continent.

The AMA was expected to be launched in 2018 (31,36), with efforts being made to ensure that the Agency capitalises on already existent mechanisms, experiences and technology to work in an effective manner towards the accomplishment of its objectives (36). It is being established by treaty to effectively address some of the challenges that are being faced by African countries. These challenges include countries having different sovereign approaches to their legal and regulatory frameworks, regulatory divergence across borders, inadequate financial resources, gaps in the development of a unified regulatory science body and the lack of a competent regulatory workforce. However, at the time when this research was started, the AMA treaty had not been ratified by the minimum required number of countries for its establishment. Therefore, in-depth research must be done to analyse the motivation of individual AU Member States to sign and ratify the AMA treaty, and the enabling factors and challenges involved. In addition, the experiences and agenda setting processes of the AU Member States that have ratified the AMA treaty should be examined in order to draw important lessons for countries that are attempting to sign and ratify the AMA treaty.

From a global perspective, the domestication and implementation of the AU Model Law and the establishment of the AMA also contribute to the attainment of the Sustainable Development Goals. Therefore, it is important to carry out an assessment of the domestication and implementation of the AU Model Law as part of monitoring and evaluation of the AMRH Strategic Framework, and to interrogate progress to date of the establishment of the African Medicines Agency, as it directly impacts regional and continental frameworks and goals. This research will potentially provide well-founded, scientific and evidence-based results that can be used for policy synthesis. More importantly, the AU

Model Law and the AMA hold promise to address gaps and inconsistencies in national regulatory legislation as well as ensure effective medicines regulation by galvanising technical support, regulatory expertise and resources at a continental level. No research has been conducted on the implementation of the AU Model Law and the establishment of the AMA. The investigators therefore intend to add to the scientific body of knowledge in this regard by carrying out an in-depth analysis of these subject matters. African people must have access to essential medical products and health technologies that are quality-assured, safe, efficacious and affordable as part of Agenda 2063 efforts.

1.4 Research Questions

1. What are the enabling factors and challenges encountered in domesticating and implementing the AU Model Law on Medical Products Regulation in AU Member States?
2. What are the enabling factors and challenges encountered in signing and ratifying the treaty for the establishment of the African Medicines Agency?
3. What is the agenda setting process leading to the ratification of the treaty for the establishment of the African Medicines Agency?

1.5 Aims

The aims of the study are to analyse in-depth the rationale, perceived benefits, enabling factors and challenges of domesticating and implementing the AU Model Law on Medical Products Regulation by AU Member States and of the establishment of the African Medicines Agency.

1.6 Specific Objectives

1. To determine the perceived benefits of domesticating and implementing the AU Model Law by AU Member States
2. To determine the challenges encountered by AU Member States in domesticating and implementing the AU Model Law
3. To assess the enabling factors for AU Model Law domestication and implementation in AU Member States that have done so

4. To determine the perceived benefits of signing and ratifying the treaty for the establishment of the AMA
5. To analyse the enabling factors and challenges encountered in signing the AMA treaty
6. To examine the agenda-setting process leading to the ratification of the treaty for the establishment of the AMA, using AU Member States that have done so as case studies

1.7 Thesis Outline

Chapter One introduces the research study and describes the study background, the rationale for conducting this study, the research questions, study aim and specific objectives, as well as the study hypotheses. Parts of the study background has been published in a peer reviewed journal (69).

Chapter Two reviews the literature on National Medicines Regulatory Authorities (NMRAs) in general and then focused on NMRAs in Africa, global medicines regulatory harmonisation initiatives, the harmonisation of medical product regulations in Africa and harmonisation in regional economic communities, Regional Centres of Regulatory Excellence, the perspectives of the pharmaceutical industry regarding medicine registration processes and regulatory harmonisation initiatives, the potential benefits and challenges of regulatory harmonisation in Africa, as well as literature on the African Union Model Law on Medical Products Regulation and the African Medicines Agency. Parts of this chapter have been published in a peer reviewed journal (69).

Chapter Three describes the study design and method used to conduct the study, including rigour and ethics considerations.

Chapter Four presents the findings of the study.

Chapter Five discusses the findings of the study, with reference to the literature that was reviewed.

Chapter Six draws conclusions about the study and provides recommendations. Some of the recommendations stated in this thesis have been published in peer reviewed journals (69,70).

1.8 Summary

This chapter introduced the research study. First, the study background was described, including the challenges faced by healthcare systems in Africa related to access to medical products. Among other factors, the challenges have partly been attributed to weak or absent medicines regulatory systems. The medicines regulatory harmonisation initiatives that are being implemented on the continent to address these challenges were also discussed. In addition, the rationale for conducting this research was discussed. The research questions, study aim and specific objectives were then presented. An outline of the thesis was also provided. The next chapter will review the literature on national medicines regulatory authorities, regulatory harmonisation initiatives, the AU Model Law on Medical Products Regulation, and the African Medicines Agency.

CHAPTER 2

LITERATURE REVIEW

3.1 Introduction

In reviewing the literature, this research study first looked at National Medicines Regulatory Authorities (NMRAs) in general and then focused on NMRAs in Africa. Global medicines regulatory harmonisation initiatives were also reviewed. These include the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, the European Medicines Agency, as well as other medicines regulatory harmonisation collaborations. Furthermore, literature on the harmonisation of medical product regulations in Africa and harmonisation in RECs was reviewed. This literature review also looked at the perspectives of the pharmaceutical industry regarding medicine registration processes and regulatory harmonisation initiatives, as well as the potential benefits and challenges of regulatory harmonisation in Africa. Moreover, publications on the African Union Model Law on Medical Products Regulation and on the African Medicines Agency were reviewed. It must be noted that there is limited empirical evidence was available on the topic and this served as the main motivation for conducting this research study. The literature that informed this chapter is therefore based on published, peer-reviewed narrative reviews, current opinions, commentaries, conference proceedings, Editorial pieces, and a collection review. It is also based on postgraduate theses, as well as AU, AUDA-NEPAD and WHO documents, articles, concept papers and press releases found in the public domain. Lastly, two theoretical frameworks are presented in this chapter which were selected for this research study.

3.2 National Medicines Regulatory Authorities

3.2.1 The Role of National Medicines Regulatory Authorities

The establishment of medicines regulatory authorities, and the realisation that medicines oversight is a necessity, has a rich history dating back to 1540 when the “Apothecary Wares, Drugs, and Stuffs Act” came into existence in England (38). National Medicines Regulatory Authorities (NMRAs) were first established in Britain (1880s), Switzerland (1900), the United States of America (1906),

Norway (1928) and Sweden (1934) (9). Their focus was mainly on patent protection and the promotion of trade; however, the laws in Norway and Sweden also focused on product safety (9). It has also been acknowledged that the requirement for medical product regulation has in most cases been a result of tragic events e.g. the Thalidomide disaster of the early 1960s catalysed the establishment of NMRAs and the subsequent review of medicines regulation to avoid a repeat of such an event. This disaster involved thousands of babies being born with phocomelia after their mothers had ingested thalidomide to treat nausea (71). Following this disaster, the World Health Organization (WHO) and its Member States called for medicines to undergo rigorous testing during the development phase and post-marketing. The Kefauver-Harris Drug Amendments Act in the United States of America (USA) was also inspired by the Thalidomide disaster and in other countries, similar legislation was passed which mandated pharmaceutical manufacturers to demonstrate that medicines are safe and effective prior to being granted marketing authorisation (72). In addition, 100 people in the USA lost their lives after they ingested sulphanilamide elixir, which then prompted the Pure Food and Drugs Act, 1938 to be passed and it required every product to undergo safety assessments before being sold (73). Since then, there has been an increase in the scope of the pharmaceutical industry and scientific knowledge, and NMRAs, their laws and regulations have also grown in terms of number, breadth, and complexity worldwide (38). In all countries, medical products are a complex, crucial component for healthcare delivery and they should be highly regulated as they play a critical role in society (9). As it stands, medical products cannot be sold in most countries without marketing authorisation from the respective NMRAs and medical devices, complementary and traditional medicines remain under-regulated in many jurisdictions, not only in Africa.

In most countries, oversight of medical products is a function of regulations or laws governing medicines which relate to the regulation and control of a number of elements of the pharmaceutical value chain, ranging from the registration of the medical products to how patients access these medical products (8). In addition, these regulations outline the functional and operational structures of the

NMRA as well as define roles and responsibilities, structures for reporting, and funding (8). Legislation and regulatory frameworks provide national governments the mandate to regulate medical products, health technologies and research in their country, through the NMRAs (13–16). The regulation of medical products that are marketed in a country includes pre-approval scientific assessments to ensure citizens have access to quality-assured, safe and efficacious medical products (16,19,31). For the effective delivery of regulatory functions to occur, comprehensive policy and legislative provisions must be available coupled with the ability to effectively manage and translate them in a manner that guarantees the protection and promotion of public health (13,18). However, the comprehensiveness of regulatory legislation, the respective NMRA's strength, and regulatory capacity differs from country to country (7,13–15). Regardless, a number of countries have developed action plans for the implementation of their national regulatory legislation (15).

Every country needs an assured supply of quality, safe, efficacious and affordable medical products (9), and the effective regulation of medical products protects and promotes public health (9,18,31,36,38,48). It also ensures the availability of high quality medical products (34). Therefore, the regulation of medical products, as a crucial element of the public health system, ensures that medical products in circulation are quality-assured, safe and efficacious, and reach patients, delivered by healthcare professionals, together with the requisite information about their rational use (6,18,31,74). Regulation does this through the enforcement of legislation, standards and norms (17,31,36,48). Additionally, medicines regulation ensures that medical products are manufactured, stored, distributed and used in line with international best practice (17,18). Sound and effective regulatory systems also promote trade and socioeconomic advancement (9). Dysfunctional NMRAs potentially (i) expose the public to unsafe medical products characterised by variable quality and efficacy, (ii) facilitate the proliferation of Substandard and Falsified (SF) medical products, and (iii) prevent the rational use of medical products, all of which jeopardise public health and patient safety (9). NMRAs, as a crucial government institution, ensure access to quality-assured, safe and efficacious medical products, therefore combatting SF

medical products (7,14,15,23,25). NMRAs have the mandate to regulate medical products and enforce regulatory functions in the discharge of their day to day duties (6,18,26). To efficiently regulate medical products, NMRAs need sufficient capacity to do so and this involves having a clear legal mandate, quality management systems, human and financial resources, infrastructure and enforcement systems (3,34,36,48). Furthermore, NMRAs provide an important public function in every country and must therefore be transparent. Transparency is a crucial aspect in the promotion of accountability in the selection of essential medicines, quality assurance, improvement of use, and research and development priority setting (56).

Medicines regulation is the totality of all legal, administrative and technical measures which governments take to ensure the quality, safety and efficacy of medical products. This also involves the assessment of the relevance and accuracy of information (19). Effective medicines regulation is a shared enterprise: a complex mix of functions (19,75). NMRAs perform a number of functions which include:

i. ensuring that there is proper licensing for the manufacture, import, export, distribution and wholesaling of all medicines, and that these activities all conform to Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP) on all premises (8,9,13–15,18,23,24,75);
ii. granting Marketing Authorisation (MA) after conducting assessments for quality, safety and efficacy of all medical products (8,9,14,15,19,23,24);
iii. ensuring that the public is not consuming SF medical products by conducting ongoing monitoring and surveillance of medical products that are on the market (8,9,19,24,75);
iv. safeguarding against the illicit trade in medical products through the inspection and control of the informal market, which includes Internet based trading (8);
v. approving the promotion and advertising of medical products (8,9,18,24);
vi. taking part in information sharing activities and forums on issues that are of common interest with regional and international regulators; and

vii. carrying out periodic monitoring and evaluation activities and taking corrective action when necessary (8).

In most countries, NMRAs have the mandate to ensure that medical products in their country are quality-assured, safe and efficacious, in addition to regulating clinical trials, manufacturing, and medical product marketing (9,13–15,18,23,24). For effective medical product regulation to occur, there is a need to have a comprehensive legal basis with appropriate and adequate governance mechanisms, robust technical expertise and scientific tools, sustainable financing, regulatory activity coordination, and performance assessments through continuous monitoring and evaluation (9). However, due to the weak implementation of regulatory legislation and gaps in the allocation of resources, the majority of NMRAs have inadequate funding and financial resources, limited expertise, low staff numbers, are overburdened, and have incomplete or incoherent policy frameworks (14,15,34). Consequently, NMRAs tend to have inadequate experience and expertise to offer to product developers who seek guidance on clinical trials and the registration of products (15). There is also a lack of adequate control over a variety of medical products that are being investigated, introduced or used in the different territories (15). To overcome some of these challenges faced by NMRAs globally, a significant number of NMRAs rely on approvals from Authorities referred to as "Stringent Regulatory Authorities" (SRAs), e.g. the European Medicines Agency (EMA), the United States Food and Drug Administration (USFDA), and WHO, for product registration guidance due to decisions of global financing bodies, particularly for AIDS, TB and malaria, relying on SRA approval of generic medicines. The controversial SRA concept is being replaced by the concept of "WHO-listed authority". In NMRAs that have insufficient capacity, there are still costly product developments and introduction delays, even with the aid of SRAs and WHO, with a resultant negative impact on patients who require those treatments (15).

For there to be effective structuring of regulatory functions, there is a need to have activities that are mutually reinforcing, including allowing different

stakeholders with different socioeconomic, policy and political intentions to interface (6). These stakeholders include manufacturers, distributors, consumers, healthcare professionals, researchers and government officials (6). As a result, the effective regulation of medicines that guarantees the protection and promotion of public health is a complex undertaking, needing the application of robust, evidence-based medical, scientific and technical know-how within the context of an appropriate legal framework (6,13,19). NMRAs obtain their power to perform a function on a legal basis and for optimum performance to occur, there is a need for a level of autonomy in executing their mandate, structures for regulatory activity coordination, financial resources as well as competent and adequate human resources (9).

3.2.2 National Medicines Regulatory Authorities in Africa

Medical products are essential for healthcare and must be accessible to the citizens of every country (17). Access to medical products, which requires a critical mass of skilled personnel, has three pivotal dimensions which all need to be addressed for any meaningful change to occur and be seen: therapeutic access, financial access, and physical access (13). However, in Africa, access to quality-assured, safe, efficacious and affordable medical products has posed a significant challenge to public health for decades (6,7). There are of course several important factors that determine access to medical products including treatment policy, pricing, procurement, as well as regulatory submissions and approvals, and product registration/approval is only one step in medication access for a patient (5).

The healthcare system grapples with severe challenges that have a negative impact on access to quality, affordable healthcare and results in morbidity and mortality from conditions that can be treated (8). In addition, there are outdated systems for filing and executing administrative work, and the human and institutional capacity challenges faced in many NMRAs go beyond inspector shortages to include absent or ill-equipped laboratories for monitoring (6,8,20). Furthermore, there is inadequate capacity to assess the safety and efficacy of

medical products as well as to continuously conduct pharmacovigilance activities (20).

Medical product regulation continues to be an important but overlooked element of public health protection and promotion (18). Although WHO recommends NMRAs to regulate all types of medicines, of 26 NMRAs in Africa, 65% have a mandate to control veterinary medicines, 69% have provisions for traditional/herbal medicine regulation, 65% regulate a broad range of products including foods, pesticides, bottled water, cosmetics and/or animal food supplements, and only 15% have the mandate to perform all regulatory functions (9). Regulatory approaches and needs differ as a result of the pharmaceutical industry size, resource base, general development levels, economic development, infrastructure, prevailing healthcare systems, research capacity, and political commitment (13,18,19). In addition, the absence of harmonised technical requirements in many African countries, the lack of capacity to regulate medical products, and differences in legal provisions of critical regulatory functions and practices impede timely access to essential medical products in some markets (9,16,30,31). The 55 African countries all have their own territorial jurisdictions and when not harmonised, a complex, inefficient and ineffective regulatory environment emerges that creates non-tariff barriers, ultimately impacting the availability and affordability of quality-assured, safe and efficacious medical products (3). As not all the countries implement a comprehensive medical product evaluation and registration system, regulatory differences related to registration systems are inevitable (19). The fragmented regulatory approach and these diverse requirements developed at country level have decreased the speed of access to medical products and increased complexity without any accompanying increase in regulatory oversight (53). Furthermore, the absence of harmonised regulations may contribute to registration timelines, regulations, costs and procedures that are different from one African country to the other which can potentially deter manufacturers from registering medical products in certain African markets (5,31). The discrepancies between regulatory frameworks and procedures on the African continent places an additional burden on both innovator and generic pharmaceutical manufacturers to adapt MA requirements

to the different NMRAs' particularities, which in itself is an added expense (5,10). For the manufacturers and MA applicants, there is an efficiency loss and for the overburdened NMRAs, there is considerably inefficient duplication of effort, resulting in further delays for patients who need the medical products (10). As a result, the removal of bottlenecks that delay access to medical products and the reduction of regulatory process redundancies is crucial (37).

To ensure accountability for decision making, transparency and independence, there is an expectation for entities that coordinate and oversee the implementation of medical product regulation to be autonomous and full-fledged departments with statutory authority in the form of boards or commissions (26,36,48). However, there are varying NMRA corporate profiles in Africa as some are lawfully established as body corporate whereas others operate as departments or units under their respective Ministry of Health (9,26,36,48). The 54 NMRAs in Africa have variable functionalities and they are at different growth, expertise and maturity levels (9). The 'maturity level' concept is incorporated in the Global Benchmarking Tool (GBT) used by WHO to objectively evaluate regulatory systems (27). The GBT allows WHO and NMRAs to assess the regulatory system's overall maturity on a scale of 1 (the existence of some regulatory system elements) to 4 (operation is at an advanced performance level and there is continuous improvement) (27). Africa has no NMRA operating at maturity level 4. However, the NMRAs of Tanzania, Ghana, Egypt, Nigeria, and South Africa operate at maturity level 3. Tanzania, Ghana, and Nigeria have maturity level 3 status for medicines and imported vaccines whereas Egypt and South Africa's maturity level 3 status is for vaccines regulation (locally produced and imported) (28,29). The NMRAs of these five countries represent effective regulatory systems on the African continent. Other African NMRAs are currently being assessed (28,29). All NMRAs on the continent eventually report to either the Ministry of Health as the overall responsibility lies with the Minister of Health (9), or they report directly to the Executive. Regardless of the differences in organisational structures and remits, NMRAs in Africa have for many years managed a diverse range of responsibilities and issues affecting medical product regulation, most of the time with limited resources (17). However, their need to

perform all the regulatory functions stipulated by law has resulted in increased strain on the already scarce resources that are at their disposal, with no significant impact on public health (18). Their focus has mainly been ensuring that the populations that they serve have access to a considerable range of affordable essential medical products, which are usually multi-source generics, and little emphasis has been placed on speedy access to the latest medical products (17). As a result, NMRAs in Africa may have experience in the management of generic medical products and have limited experience in the assessment, approval and registration of innovator medical products, a significant majority of which are for chronic conditions such as diabetes, hypertension and cancer (17).

Some of the existing and emerging medicine registration issues in Africa include the regulation of biosimilars and vaccines, advancements in medical products, clinical trial regulation and the establishment of clinical trial registries, blood and blood product regulation, and regulation of medical devices, especially diagnostic agents (13,17,25). The increase in the number of medical products needing registration will potentially result in extended backlogs for product introduction as the medical products have complex manufacturing processes, NMRAs in low- and middle-income countries (LMICs) have inadequate evaluation expertise, and there may be a need for specific regulatory systems (15,25). However, if regulatory systems in LMICs are strengthened in value-added ways, it allows for reliance, work sharing, and promotes a harmonised approach as part of ensuring universal access to quality healthcare (25). Despite these issues, it is worth noting that NMRAs are not expected to perform all the regulatory functions on their own as there is scope for reliance and recognition pathways (3,74). For instance, GMP compliance can be assured in a more resource efficient manner through the recognition of SRA inspections and the mutual recognition of African NMRA inspections (37). The need for duplicative inspections can be negated by a positive inspection report or an SRA's valid GMP certificate (37). To some extent, having inadequate resources may be compensated by countries effectively collaborating and sharing information (19).

Regulators in Africa are challenged by the problem of SF medical products (13), which includes inadequate/over-concentration of ingredients, contamination, low quality ingredients, poor stability and unsuitable packaging (19). In addition, SF medical products exist because medical products manufactured for export purposes may not be regulated to the same standard as when they are intended for domestic purposes, and NMRAs in low-income countries may not be adequately equipped to prevent or rectify the problem (19). In the majority of countries, there is inadequate capacity which serves as a barrier to accessing quality-assured medical products and results in the proliferation of SF medical products (3,6,13,14,25,36,48,49). These SF products are used in high volume for the management of conditions of public health interest, for instance anti-malarials, antibiotics, antihypertensives and antidiabetics (13). SF medical products are found in countries that have promising capacities in pharmaceutical production but with weak NMRAs (7,13). The pharmaceutical markets in Africa are generally poorly regulated which presents a public health risk and diminishes the public's confidence in the healthcare delivery systems (13,18). SF medical products are a global concern and compound the issue of timely access to quality-assured medical products, especially in LMICs where they are estimated to constitute a minimum of 10% of the medicines in circulation (25). The existence of SF medical products in any country threatens patient safety, results in a loss of confidence in the health system, increases treatment failures and antimicrobial resistance, as well as costs LMICs approximately US$31 billion annually (19,25,49). The absence of an enabling regulatory environment has also negatively impacted local pharmaceutical production in Africa (3,8). Therefore, before a country builds its pharmaceutical industry, it must first strengthen its medical product regulations (13).

In another study conducted which involved 20 Sub-Saharan African countries, the results showed that it took an average of 78 months for the first and the last registration of 8 vaccines, and new drug registrations take an average of 52 months which is also lengthy (35). The worldwide status quo of divergent regulatory requirements and registration processes requires regulatory groups of pharmaceutical companies to tailor a CTD for each territory where they seek

medical product registration (35). Basically, this is submitting the same information in different formats, which does not translate to significant value addition, if any (35). This presents an opportunity for higher level alignment (35). Additionally, there are delays of 4-7 years between first regulatory submission to a well-resourced NMRA and final approval in SSA (5,9,10). Pharmaceutical companies have declined to supply medical products to certain African markets and they have cited these lengthy registration times as one of the reasons (9). Some of the barriers that cause these delays are lengthy processes for medical products registration that result in delayed approvals, general resource constraints, and failure to leverage regulatory review activities that have been carried out by SRAs or WHO (10). Furthermore, clinical trial authorisations are delayed by the absence of role clarity or transparency between the NMRA and the National Ethics Committees (10).

One of the criteria used to assess pharmacovigilance (PV) systems in a country is membership to the WHO Programme for International Drug Monitoring (PIDM) (9). In order to gain membership, the requirements are to have a designated national PV centre, a spontaneous adverse drug reaction (ADR) reporting system, and submitting at least 20 reports to the WHO individual case safety report (ICSR) database, VigiBase™, as a demonstration of technical competence in the management of ICSRs (9). In 2000, there were 5 countries in Africa that were WHO-PIDM full members, and in 2015 the number had increased to 35 countries with the main ICSR reporting countries being South Africa, Morocco, Nigeria, Egypt and Kenya (9). There is a need for a more robust PV system in Africa because, despite weak health systems and the absence of resources, millions of doses of medicines and vaccines are deployed to address priority diseases (9). 72% of countries in SSA also have quality control laboratories albeit at different developmental levels, and 63% are engaged in market surveillance (9).

Within their specific national contexts, regulators are increasingly having to focus on activities that add the most value with regard to public health protection and promotion and protection (30). Evidently, interventions are required to prevent widening the gap that exists between African NMRAs and NMRAs of high-

income countries, and the healthcare needs of their respective populations (17). While these challenges prevail, interventions that can positively and effectively improve health outcomes exist (36). For NMRAs to fulfil their statutory legal and regulatory functions, their capacities need improvement and in countries where considerable resource constraints exist, information and facility sharing for medicines registration is encouraged (26).

There have been several efforts, including by WHO and donors, to strengthen capacity building, national and sub-regional regulatory systems and harmonisation but evidence demonstrates that the capacity of African countries to regulate medical products remains insufficient (26,36,48). Therefore, investments in regulatory systems strengthening are not only important, but are needed in order to attain mature regulatory systems (3,25). Harmonising and coordinating regulatory efforts on the continent is necessary to streamline pre-marketing authorisations, make the post marketing surveillance system more robust, create an enabling environment for local production, and improve access to medical products (3). In addition, as Africa continues to converge towards a common medical product regulatory framework, it will enable benchmarking to identify the different capacity and performance levels (9). The benchmarking of African NMRAs needs to be conducted based on agreed criteria as well as in a transparent and objective manner (9). In various aspects of health systems, the harmonisation of approaches has been seen as a potentially successful method of public health improvement, not only in Africa but globally (13). The outcome of benchmarking will support ongoing efforts in harmonisation, facilitate capacity building among NMRAs, and the sharing of best practices (9). As a result, academics, policymakers and practitioners have invested in advancement efforts towards harmonised processes and systems (13). In the field of medical product regulation, the low levels of expertise in regulatory science, high regulatory costs, the escalating prevalence of SF medical products and unregistered medical products has made the harmonisation of regulatory systems a desirable policy option (13).

3.3 Global Medicines Regulatory Harmonisation Initiatives

3.3.1 The Motivation for Global Regulatory Harmonisation

Pharmaceutical drugs are an essential component of human medicine as we know it and are developed for the diagnosis, prevention, treatment or the management of disease (76). Since the 1990s, innovation of pharmaceutical products has increased worldwide and so has access to novel treatments owing to generic products being made available (20). Over time, medical product regulations have also evolved in response to an increase in scientific knowledge and pharmaceutical industry complexity (77). To ensure that the public has access to quality-assured, safe and efficacious products, pharmaceuticals are developed to comply with the stringent regulatory requirements specified by NMRAs in different countries (76). The pharmaceutical industry aims to market its products in as many territories as possible, to provide access to medical products and to optimise its returns on investment (76). Decades ago, a localised approach was commonplace as the regulation of medical products was significantly less complex and NMRAs only had to focus on their own domestic market (34). However, in the current context, there has been increased intercountry collaborative initiatives at both the regional and international level, making borders more open for trade among countries with differences in regulatory, financial and technological backgrounds as part of the trend towards globalisation (77). The global harmonisation of pharmaceutical regulations has become essential for companies, international consumers and agencies (77). Consequently, NMRAs and industry associations have initiated collaborative work procedures to increase the harmonisation of regulatory requirements and to ensure that their regulations are as close as possible to international standards (76,77). Unless there are apparent regional and ethnicity differences, regulatory safety and efficacy standards that relate to the review and availability of new medicines should be similar (77).

NMRAs can improve regulatory oversight through regulatory harmonisation which aims to improve and streamline regulatory requirements, guidance and technical standards by transitioning from a country-focused approach to a more collaborative, multi-country approach (34). By definition, harmonisation is a

"process by which technical guidelines, formats, scientific requirements and standards are developed to be uniform across participating authorities" (34). All participants need to consent to the process of merging national standards with international standards and harmonisation does not mean participating authorities make united regulatory decisions (34). Regardless of country or region, medicines regulatory harmonisation initiatives have differences in scope, degree of harmonisation, approach and institutional level (34). Given the globalised nature of pharmaceutical production and trade, and the increasing complexity of medical products, NMRAs are facing challenges in executing their mandate (34,38). In addition, globalisation comes at a time when NMRAs face challenges due to clinical trial data being generated abroad, rapid advances in science and technology, budget constraints, bureaucracy, political backlash and an inexperienced human resource base (34,38). Due to globalisation, regulators are also experiencing an expansion of their responsibilities as supply chains become more complex, multi-faceted and globally integrated (34,38,78); they must review a lot of information, some of which they may lack the know-how to review, and monitor several processes occurring in foreign territories (34,38). As a result, regulatory harmonisation has inevitably gained popularity, particularly for highly specialised functions, and its importance is increasingly being recognised for public health protection and promotion (34). Harmonisation and globalisation of standards are potential solutions for NMRA challenges as they reduce unnecessary duplication of requirements and effort, rationalise time and costs, as well as establish transparent regulatory processes, resulting in improvements in access to novel medical products (7,19,76,77). Ultimately, a lack of regulatory cooperation and harmonisation will potentially become a barrier to medical product access (34).

Over the past two decades, the industry has expanded to become more international with research and development (R&D) being conducted in emerging markets in pursuit of better economies of scale (76,77). While this is happening, globalisation has also blurred the line between domestic and foreign pharmaceutical products (38,78). Moreover, the innovative and economic landscapes have been fundamentally transformed by globalisation (38), resulting

in the need for new strategic approaches to pharmaceutical harmonisation (77). NMRAs need a global perspective to oversight urgently as public health and innovation have ceased to be purely national concerns (38). Globalisation, which has a direct impact on public health protection and promotion everywhere (78), has several advantages, some of which are capacity building in emerging markets and improved access to quality-assured, safe and efficacious medical products for different people worldwide (76). As globalisation continues, it inevitably becomes part of pharmaceutical manufacturing and NMRAs are faced with the challenge of failing to effectively and efficiently regulate medical products individually, both for existing and new innovative medical products (3,25,33). The introduction of new medical products onto the market can have an unintended consequence of placing burdens on existent health systems, which includes needing new medical product regulatory requirements, supply and distribution, as well as capacity building through training healthcare personnel (14). In response to this challenge and regardless of whether an NMRA is well-resourced or poorly resourced, there has been an increased drive for collaboration, cooperation, the adoption of regulatory reliance models and convergence as effective strategies (3,25).

Historically, medical product regulations in different countries were being affected by local politics, economics, the availability of resources as well as country-specific public health needs and therefore evolved independently of each other (77). The NMRAs were developing their own technical guidelines and standards (76). The purpose of guidelines and standards is to provide assistance in the interpretation of regulatory requirements and help the pharmaceutical industry meet the specified requirements (76). When the different NMRAs develop their own technical standards and guidelines, it results in divergent requirements from one region to another which then impacts R&D costs and delays access to innovative medical products/health technologies (76). An obstacle to international medical product approvals is different regulatory models and processes that exist in the different countries (31). The interconnectedness of the supply of medical products and the evolving challenges that institutions as well as governments grapple with if they attempt to solve the challenges

unilaterally has catalysed increased interest in regulatory harmonisation and collaborative networks (3,13). Medicines regulatory harmonisation encourages information and technology sharing as well as promotes enhanced medicine access (20).

Drawing lessons from other sectors that have developed global regulatory initiatives, there are five distinct stages that have been followed for success: agenda setting, negotiation, implementation, monitoring, and enforcement (20). For there to be cooperation and sustainability, a multisector approach, which involves all medicines regulation stakeholders, is necessary (20). Each stakeholder will bring to regulatory affairs different strengths and resources which will enable increased capacity, communication, and trust in the regulatory system (20). In order to build regulatory capacity and trust, as well as increase confidence in outcomes of dossier assessments and strengthen their quality, especially for innovative products, institutions in LMICs and high-income countries need to network, both formally and informally (7,19). By recognising the considerable differences that exist across various harmonisation initiatives in terms of scope, degree of harmonisation, as well as approach and institutional level, it becomes a challenge to conduct a comparative analysis of which model of collaboration has, to date, been the most effective (34). Therefore, each harmonisation initiative is better off being assessed against its objectives in order to obtain a fairer analysis (34). This assessment of objectives should be embedded and it is important to anchor positive policy change as well as rectify change agents that are potential threats (13).

3.3.2 The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

Regulatory requirements differ across countries and this makes pharmaceutical drug applications and marketing a costly and complex endeavour that delays the public accessing life-saving medical products (77). In response, there have been a number of efforts over the years to align regulatory requirements between countries and regions as well as to advocate for mutual recognition between regulators of different territories, all in an attempt to avoid redundancy while

saving on time and resources (35). The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) represents one such global initiative (3,35,76). In 1989 in Paris, specific plans of action were being crafted at the WHO International Conference of Drug Regulatory Authorities (ICDRA) and soon after, the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) was approached by the authorities to discuss a joint regulatory-industry initiative on international harmonisation, thereby conceiving ICH (76,77). ICH was established in 1990 as a tripartite effort of the European Union, Japan and the United States of America and has expanded to include other countries and regional harmonisation initiatives who are now either members or observers, making ICH a truly international platform for regulatory harmonisation work (3,7,19,20,34,35,76,77). At the inaugural ICH Steering Committee meeting, it was agreed that the harmonisation topics selected would be split into Safety, Quality and Efficacy to reflect the three criteria that are the foundation of authorising new medical products (76). A notable collaborative network, ICH's primary objective is public health promotion and its mission is to achieve greater harmonisation to ensure the development, registration, and manufacture of quality-assured, safe and efficacious medical products in the most resource-efficient manner (3,76). It is worth noting that ICH was established for new innovative medical products and the founding ICH countries are highly industrialised countries that control a significant portion of the innovative industry, whereas LMICs have either no local pharmaceutical production or only conduct generic manufacture (19). In addition, the three regions benefitted, through ICH, from improvements in the development and licensing of novel medical products in a cost-effective and efficient manner (77) by reducing animal testing as well as preventing the unnecessary duplication of clinical trials in humans without any compromises in safety and efficacy (20,76,77) ICH, a non-profit organisation, does not pursue any commercial purposes and its work is complemented by other international regulatory harmonisation and collaborative initiatives, for instance the International Pharmaceutical Regulators Programme

(IPRF), the International Generic Drug Regulators Programme (IGDRP), and the International Coalition of Medicines Regulatory Authorities (ICMRA) (76).

ICH is an international initiative that provided a multiregional discussion forum for harmonisation and is dedicated to the development of harmonised technical guidelines and standards to facilitate the registration of human pharmaceuticals globally (34,76,77). Since 1990, more than 60 guidelines and standards have been developed in a number of topics and implemented across the ICH participating regions (76,77). The process of guideline development at ICH is science based, consensus driven and effectively managed to provide specific outcomes under strict timelines (76). The ICH guidelines have a focus on, and are applicable to, New Chemical Entities (NCEs) rather than generic medical products, which are more prevalent in LMICs (20). LMICs, the majority of which are not ICH members, have stated that WHO standards have more feasible implementation compared to ICH standards which have been critiqued for being more costly to implement, and need greater human and technical resources (20). One of the achievements of the ICH was developing and promoting the use of the CTD, and now the electronic CTD, which is a common regulatory submissions dossier for use in the ICH countries (7,34,35,76,77). The CTD format, which was finalised in November 2000, was developed with the intention of improving efficiency by lowering costs, and maximising human resources by reducing time to reformat medicines registration dossiers (20). Using a "common language", the CTD format also brings medical products more efficiently to the market in multiple countries which is especially important in low-income countries that lack expert resources (20). The CTD is a standardised format for pharmaceutical companies to present the Quality, Safety and Efficacy information in the new medical product's dossier which is being filed for review (76). The CTD, whose initial development was to facilitate paper filing, has harmonised the format of drug submissions, enabled the implementation of Good Review Practices, and has eliminated the need for the pharmaceutical industry to reformat submission information to the different ICH NMRAs (76). Despite the CTD being adopted for use by additional countries worldwide in an attempt to harmonise requirements, there is still a lack of harmonisation as a result of countries that

adopted the CTD making local independent adaptations to the ICH CTD template which defeats the initial harmonisation intentions (35).

To reach its current status, the ICH harmonisation process has had considerable investments in terms of time and money from the different stakeholders involved (20). However, the ICH process is considered by some authors to generally require considerably lower levels of resources to develop guidelines and standards from any individual NMRA compared to the resources that the NMRA would require if it decided to undertake this work independently (76). There is no empirical evidence to support this assertion. Following its success, the ICH process has become a good harmonisation model and ICH guidelines are perceived as the gold standard for technical standards which some countries publish in their regulations. ICH's successful model of harmonisation also sparked international interest in the harmonisation process which then led to a number of regional harmonisation initiatives developing unified standards and guidelines on quality, safety and efficacy of medical products based on ICH procedures and guidelines (77). In 1997, following the completion of the majority of its objectives, an ICH subcommittee saw the need to take steps to expand its efforts and support these regional initiatives (77). In 1999, the Global Cooperation Group (GCG) was established as a subcommittee for communication with non-ICH countries and served as an information liaison between ICH and non-ICH countries, making information on activities done by ICH and ICH guidelines available to any country/institution that was interested (77). WHO, which was invited to join and act as a link between ICH and non-ICH countries/regions, worked with the GCG as well as other international organisations to foster acceptance and subsequent adoption of ICH guidelines in non-ICH countries (77). NMRAs and the pharmaceutical industry have both enjoyed benefits delivered by ICH (76). The former has benefitted significantly from knowledge exchange, work sharing and the efficiencies gained with the ICH process and the latter has benefitted from harmonised global requirements, therefore eliminating duplicative efforts in medical product registration (20,76). Overall, when requirements are harmonised, they facilitate the development and

registration of human medical products internationally, which benefits patients the most (76).

3.3.3 The European Medicines Agency

Europe was the first to lead the most advanced initiative in regional medicine regulatory harmonisation (77) and the European Medicines Agency (EMA) is the only global example of a regional centralised regulatory system (36,48). Beginning in 1965, the European Union's harmonisation created community-wide mechanisms and clearly defined the mandate of both the Community and Member States. There was a need for a common market and the idea for harmonisation was based on the advanced national systems and supportive legal instruments already existent in the Member States (7,36,48,76). In the 1980s, the European Commission (EC) led the first attempt at harmonising pharmaceutical regulatory requirements and it was very successful in developing and implementing a regional harmonisation structure for drug regulatory laws and regulations that would then lead to the establishment of a single market and the promotion of the free circulation of pharmaceuticals within European Union (EU) Member States (77). This was accomplished by creating the European Council in July 1993 and the subsequent establishment of the European Agency for the Evaluation of Medical Products (EMEA) in 1995 (77). EMEA was established to coordinate and facilitate the harmonisation of European pharmaceutical requirements following the recognition of the increasing regulatory complexity, as well as time and costs needed for the development of new medical products (77). Essentially, for the pharmaceutical industry to be more effective in the development and marketing of medical products, it needed a streamlined regulatory environment within the EU (77). The implementation of the centralised procedure in 1995 is the most notable accomplishment of EMEA. The procedure allows applicants to submit one marketing authorisation (MA) application that is then assessed by the Committee for Medicinal Products for Human Use (CHMP), a centralised committee, which allows marketing in all EU Member States for approved products (20,77). EMEA changed its name and logo in 2010 and became the European Medicines Agency (EMA) (77).

The EMA, which is a decentralised body of the EU (34), became operational in 1995 following 30 years of efforts (3,7,36,48,77) (72), and all the member states had to accept the body of EU rights and obligations that bind the member states within the EU together, *community acquis*, and to implement the regulatory framework for accession to EMA (36,48). Through the EMA and its Heads of Medicines Agency, the EU managed to harmonise the European-regulated market (34). Europe's success demonstrated that harmonisation was a feasible venture (76). In the EU system, marketing authorisation can be applied for by pharmaceutical manufacturers using one of four available procedures described in Table 1 (72). The EMA is currently responsible for the scientific evaluation of human and veterinary medicine marketing authorisation applications that fall within the ambit of the centralised procedure (3,7,20,36,48,72). Under the centralised procedure, applications are sent directly to the EMA for review (20). The EMA's centralised procedure, which is required for several drugs and optional for others, grants MA to a new medical product and the MA will be valid for the 28 European Union countries and in the three European Economic Area countries for five years (20,23). In addition, the centralised procedure allows for diversification of skills of the participating NMRAs and provides an opportunity for learning outside the country (20).

Table 1: Pathways to obtain marketing authorisation for medical products in the European Union (72).

Pathway	**Process**	**Comments on Use**
Centralised procedure	Pharmaceutical manufacturers submit their applications directly to the EMA. Scientific expertise is then drawn from EU Member States by the CHMP to determine whether the medical product should be granted marketing authorisation.	Mandatory for most new and innovative medical products
Decentralised procedure	An initial evaluation of the medicine is performed by one EU Member State. The member state then issues a draft assessment report and other member states can then ask questions and raise objections.	Mostly used for the approval of generics in the EU
Mutual recognition procedure	This procedure is similar to the decentralised procedure. If one EU Member State has already approved a medicine, and the manufacturer is seeking marketing authorisation in at least 1 other member state, the member state that has already issued marketing authorisation will share its draft assessment report allowing other member states to ask questions and raise objections.	Mostly used for the approval of generics in the EU
National procedure	One EU Member State approves a medical product and no interaction with or recognition by another member state takes place.	Rarely used
CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; EU, European Union.		

The EMA, providing scientific advice for the centralised procedure, has a representative of each EU Member State participating in the work of the scientific committee while the EC makes marketing authorisation decisions (3,23,36,48). The EC is also responsible for implementing and overseeing the legal basis for the system, and ensuring that the system's decisions are recognised by member states (72). The EMA assessment is usually completed within 210 days (23) and the EMA's budget is based on fees paid by industry for product application evaluations and from the European Commission (3). European NMRAs conduct functions such as inspection, quality monitoring, safety monitoring, and for the 1000+ medicines that do not fall within the scope of the EMA centralised procedure, the NMRAs issue marketing authorisations for these products either individually in accordance with the procedures in their country or through decentralised/mutual recognition pathways (3,20,23,36,48). As the regulatory requirements and procedures in the EU are harmonised, the data requirements and standards are the same across MA routes (23). There are a number of models for agencies and included among them are information agencies and executive agencies (3). Information agencies have the task of information collection and dissemination as well as the management of expert networks whereas executive agencies provide specific services while performing a specific mandate (3). By nature, there is a requirement for regulatory agencies to be actively engaged in executive functions by enacting instruments for regulating a specific sector, i.e. they have the authority to engage in the adoption of individual decisions that are legally binding on third parties (3). Within the context of the EU, EMA is an information agency although in practice its opinions are containing on the Commission which hardly ever opposes the EMA (3).

3.3.4 Other Medicines Regulatory Harmonisation Collaborations

3.3.4.1 The International Generic Drug Regulators Programme (IGDRP)

The International Generic Drug Regulators Program (IGDRP) was established by a group of regulators in 2011 and was initially launched as a 3-year pilot program with the objective of generic drug regulatory convergence and cooperation in order to address challenges that stem from increased workloads, globalisation and

the complexity of scientific issues (3,20,34). As part of broader international regulatory efforts, the results of the pilot would influence decisions on the creation of more permanent information and work-sharing initiatives (20). Information sharing is recognised as an important element of regulatory convergence, as well as the need for the establishment of electronic platforms for non-confidential data and secure platforms for confidential data exchange (20). The pilot also sought to provide an efficient and consistent review procedure while attaining a reduction in the regulatory burden and enabling similar timing of marketing authorisations in multiple territories (3). Applicants were invited, through an expression of interest, to use the IGDRP for work-sharing in the review of applications for the registration of generic medical products in Australia, Canada, Chinese Taipei, Switzerland and the EU (3). Since 2014, IGDRP has become a permanent programme aimed at facilitating timely authorisations and the availability of quality-assured, safe and efficacious generic medical products (34). IGDRP also has intentions of expanding its scope to include biosimilars in the future (34). The countries and organisations currently participating in the IGDRP are Australia, Brazil, Canada, China, Chinese Taipei, the European Directorate for the Quality of Medicines and Healthcare, Japan, Korea, Mexico, New Zealand, Russia, Singapore, South Africa, Switzerland, the USA and WHO (3,34). The working groups of IGDRP focus on "Active Substance Master Files/Drugs Master File (ASMF/DMF)", "Biowaivers" and "IT business needs" (34).

3.3.4.2 International Coalition of Medicines Regulatory Agencies (ICMRA)

International collaborative approaches are a necessity in response to the increasingly complex medical products, ingredients and associated risks or benefits (78). There is a need for these international collaborative approaches to provide access to NMRAs' resources and the best available scientific/technical expertise (78). As a result, discussions had been ongoing for years including at the World Health Assembly (WHA), the WHO's International Conference on Drug Regulatory Authorities (ICDRA), and the International Summit of Heads of Medicines Regulatory Agencies (78). Finally, in December 2013, the

International Coalition of Medicines Regulatory Agencies (ICMRA) was established at the Summit of Heads of Medicines Regulatory Agencies in Amsterdam and it complements the operational/technical work of the IGDRP as well as other international generic medicines collaborative initiatives (3). A voluntary leadership group at the highest executive level (38,78), the Coalition has the intention of creating a broad, formal framework which NMRAs can use to enhance communication, collaboration, regulatory alignment, information sharing and crisis response (38,78). In addition, in this increasingly complex and globalised regulatory environment, ICMRA brings senior NMRA leadership together to provide consistent, coordinated, strategic high-level advocacy and leadership to address current and emerging global regulatory challenges and to better leverage resources in a manner that can expand global regulatory reach (78). ICMRA focuses on work at a strategic and policy level as well as on developing governance models and regulatory programs (3). Furthermore, ICMRA provides guidance for a variety of activities that are common to NMRAs' goals and missions, identifies areas for potential synergies, and leverages existent efforts to maximise global impact (78). Members of ICMRA are Australia, Brazil, Canada, Italy, France, Germany, India, Indonesia, Ireland, Japan, Mexico, Netherlands, New Zealand, Nigeria, China, Russia, Singapore, South Africa, Sweden, Switzerland, the United Kingdom, and the USA (3). ICMRA also has EMA, EC and WHO representatives (3).

3.3.4.3 The Role of WHO in the Regulation of Medical Products

WHO has 193 member states and it is an international, intergovernmental, specialised United Nations agency (77). It is the only organisation with a legal international mandate from member states to set international standards for the protection and promotion of public health (77). Since the early 1970s, WHO has been providing guidance and assistance to NMRAs of low-income countries on regulatory systems strengthening and infrastructure set-up (77). In addition, since 1980, WHO has been convening the International Conference of Drug Regulatory Authorities (ICDRA) biennially as part of its efforts to support global harmonisation (77). ICDRA offers a platform for NMRAs of WHO member states to communicate, coordinate and collaborate amongst themselves (34,77).

The ICDRA's objectives are: (i) to promote collaboration among NMRAs, (ii) to reach a consensus on issues of common interest, (iii) to facilitate timely and adequate information exchange, and (iv) to discuss internationally relevant issues (77).

WHO plays a crucial role in spearheading harmonisation of quality, safety, efficacy and nomenclature requirements worldwide (77). WHO also establishes medicinal, clinical, and technical standards as well as promotes regulatory capacity building, training, and work sharing for NMRAs (34). The WHO Collaborative Procedure, a collaboration between the WHO Prequalification of Medicines Programme (WHO-PQP) and interested NMRAs, can be used for assessment and expedited national registration of pharmaceutical products that are WHO prequalified (31). The WHO-PQP, which was set up in recognition of systems in LMICs being ill-equipped to perform assurance functions, certifies medical products for priority diseases and provides guidance on purchasing medical products to participating countries and procurement agencies (74). At the request of the manufacturer, confidential WHO-PQP assessment and inspection outcomes can be shared with participating NMRAs through a secure Internet-based platform, subject to agreed restrictions on use and confidentiality agreements (3). There are 25 countries that participate in the WHO Collaborative Procedure and 22 of them are African (3). From inception, capacity building has been one of the main objectives of the WHO-PQP and the programme, to execute this objective, has leveraged the best available national regulatory expertise while pro-actively including and involving NMRAs from LMICs (19).

3.3.4.4 Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S)

The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S), two international instruments between governments and pharmaceutical authorities, encourage the mutual recognition of manufacturing site inspections and has 46 participating authorities, of which South Africa is the only member from Africa (3,34). The objective of PIC/S is to spearhead the international development, implementation and maintenance of

harmonised GMP standards and quality systems of inspectorates in the medical products field (3). PIC/S also provides an active and constructive cooperation in ensuring GMP (3).

It is evident that regional harmonisation initiatives offer different working models, methods of exchanging regulatory information, creating common technical requirements, and pooling information on medical products post-marketing (19). Table 2 highlights some of the regulatory harmonisation initiatives from around the world. Other collaborative frameworks that exist that were not discussed in this section include the Access Consortium, International Regulatory Cooperation for Herbal Medicines (IRCH) Working Group, Regulatory Cooperative Initiative between Canada and Australia on work sharing activities, and European Community-Australia Mutual Recognition Agreement.

Table 2: Examples of regulatory harmonisation initiatives from around the world (72).

In Africa	Outside Africa	Global
• Arab Maghreb Union • The East African Community's Medicines Regulatory Harmonisation initiative • Economic Community of Central African States – Organization of Coordination for the Fight Against Endemic Diseases in Central Africa • Economic Community of West African States – Union Economique et Monetaire Ouest Africaine • Intergovernmental Authority on Development – Community of Sahel-Saharan States • South African Development Community – Common Market for Eastern and Southern Africa, including the Zazibona Collaborative Medicines Registration initiative	• APEC's Life Sciences Innovation Forum – Regulatory Harmonisation Steering Committee • ASEAN's Pharmaceutical Product Working Group and Medical Device Committee • EU system, including the EMA • Gulf Health Council • Pan-American Network for Drug Regulatory Harmonisation	• ICH

APEC, Asia-Pacific Economic Cooperation; ASEAN, Association of Southeast Asian Nations; EMA, European Medicines Agency; EU, European Union; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

3.4 The Harmonisation of Medical Product Regulations in Africa

3.4.1 The African Medicines Regulatory Harmonisation Initiative

As a way of enhancing aid effectiveness in the health sector of low-income countries, there have been calls for the increased use of horizontal development cooperation mechanisms such as South-South Cooperation (SSC), which has resulted in the increased implementation of new models of development cooperation (79). The calls are often influenced by the use of controversial terms such as North-South Cooperation (NSC), and the need for self-determination, solidarity, as well as sustainable locally-engineered development and aid effectiveness among countries of the global south (79). Historically, SSC meant the process of knowledge exchange and resources among countries of the Global South and now it is seen as a means to ensure equity between the Global South and the Global North, and as an opportunity to overcome the legacy of colonial aid (79). In 2009, a High Level UN Conference provided the following comprehensive operational definition of SSC: "a process whereby two or more developing countries pursue their individual and/or shared national capacity development objectives, through the exchange of knowledge, skills, resources and technical know-how and through regional and interregional collective actions, including partnerships involving governments, regional organisations, civil society, academia, and the private sector, for their individual and/or mutual benefit within and across regions" (79).

In Africa, the health development aid flagship is NSC and it is often accompanied by inappropriate technology, a lack of understanding of the local context and realities on the ground, as well as a lack of equality in the partnership, which further calls for increased horizontal partnerships among Global South countries (79). Given the similarities in the health and development contexts of African countries, the foregoing emphasises the need for streamlined collaboration, experience sharing and capacity building among African countries (79). Cooperation, as an effective tool for countries, can strengthen and catalyse health development, facilitate knowledge and experience sharing for health improvements, and ensure efficient use of existing resources within countries and across regions (79). SSC, which is an opportunity for regional integration

strengthening, can be demonstrated in the production of essential medicines, medical products, vaccines, regulatory harmonisation, institutional capacity building and health workforce development (79).

The world, divided by technology and not by ideology, has about 15% of the population historically leading and predominantly providing all global technological innovations (21). Another part of the world, approximately half of the world's population, were adopting these technologies in terms of both production and consumption (21). The remaining one third of the world which included Africa was technologically disconnected, and they neither engaged in domestic innovation nor adopted technologies from abroad (8,21). In response to this, Africa's leaders embarked on a journey to change this narrative and created a flagship program of the African Union (AU): the New Partnership for Africa's Development (NEPAD) Planning and Coordinating Agency (NPCA) (21). NPCA would later transform into NEPAD Agency, and it is currently known as the African Union Development Agency NEPAD (AUDA-NEPAD). As the technical arm of the AU, the NPCA sought to end poverty, put African countries on a sustainable growth and development path, and enable Africa to participate in the booming global bio-economy (21,37). As part of the process of attaining these objectives, the NPCA established two pivotal and fairly related programmes, which were the African Medicines Regulatory Harmonisation (AMRH) initiative and the African Biosafety Network of Expertise (ABNE) (21). These programs, which were implemented on the platform of the NPCA's Industrialisation, Science, Technology and Innovation Hub, support African countries to craft regulatory environments that enable science, technology and innovation to flourish, particularly for agricultural and health applications (21).

The AU, focused on leading the development and integration of Africa, has a vision of "an integrated, prosperous and peaceful Africa, driven by its own citizens and representing a dynamic force in the global arena" (3). AU Member States are all independent countries that are organised into a number of sub-groupings, including RECs and trading blocs, with overlaps and membership in several RECs and trading blocs being a common occurrence (8). Compounding

the complexity of multiple memberships of several AU Member States is the considerably different disease profiles and pharmaceutical sector specific challenges in North Africa compared to Sub-Saharan Africa (SSA) (8). The AU aims to accelerate regional integration, while the NEPAD Planning and Coordinating Agency (NPCA), as the African Union's socioeconomic development programme, facilitated and coordinated the development of continental as well as regional programmes/projects that are of high priority, and bridged the existing development gaps with the goal of rectifying the socioeconomic, political and environmental factors that undermine public health (14,18). The NPCA had the mandate to:

i. mobilise resources and partners in support of the implementation of priority programmes/projects in Africa;
ii. Execute and coordinate research as well as engage in knowledge management;
iii. Monitor and evaluate the implementation of programs/projects; and
iv. Advocate for the AU and NEPAD's vision, mission, core principles and values (18).

As part of these goals, the African Economic Community (AEC), more commonly referred to as the Abuja Treaty has been in operation beginning in 1994 and pursues the creation of an African Common Market through the use of RECs as 'building blocks' (3,21). Over the last five decades, various changes and alignments have happened in Africa and among these have been the establishment of RECs (37). In Africa, there are 8 RECs: Arab Maghreb Union (UMA); Common Market for Eastern and Southern Africa (COMESA); Community of Sahel-Saharan States (CEN-SAD); East African Community (EAC); Economic Community of Central African States (ECCAS); Economic Community of West African States (ECOWAS); Intergovernmental Authority on Development (IGAD); and the Southern African Development Community (SADC) (51). These RECs cluster individual countries into sub-regions with the objective of attaining better economic integration as well as to coordinate the implementation of NEPAD Agency programmes (3,21). RECs also promote

common trade, economic development, and market opportunities to their respective member states (16,18). In addition, RECs are engaged in the promotion of social development and are increasingly involved in healthcare (16,18). Alternatively, RECs can be viewed as independently formed geographical groupings of African countries with the intention of promoting the integration of mutual regional interests and processes, such as the common goal of healthcare sector improvements in the respective regions (37). The RECs, which create a common marketplace, potentially offer significant economies of scale that can be realised through the adoption of collaborative approaches to regulatory functions (3). As RECs offer a collaboration opportunity across the AU, its developments are therefore not only important to the region, but to Africa as a whole (37). Since 2006, the AMRH initiative has been working in medicines regulatory harmonisation which has resulted in the development of several regional harmonisation proposals in a number of RECs as a way of building upon and strengthening plans that are existent in sub-regional groupings (8,26). NEPAD, and the Consortium members, have been working with RECs to ensure that all efforts are complementary and enable continent wide communication, coordination and technical consistency as well as for the mobilisation of donor support (26). Through the RECs, the AMRH initiative has established a regional platform for medical products and health technologies' regulation which can be utilised for the building of trust, confidence, as well as ownership and alignment, especially for countries that are in the process of building systems for medicines regulation (3,21).

Since October 2008, AUDA-NEPAD has been responsible for the coordination of the AMRH initiative as part of the implementation of a resolution of the African Ministers of Science & Technology and Ministers of Health (18). In February 2009, NEPAD in collaboration with the Pan African Parliament (PAP) convened a conference in Johannesburg of RECs and NMRA representatives with the aim of exploring the value and potential for the harmonisation of medical products registration (16,18,20). The AMRH initiative, which was conceptualised in 2009, was motivated by the need to remove obstacles preventing access to medical products for patients in Africa (10). The AMRH

initiative was then formalised in the same year (7,9,31,40), and aimed to improve the health of the population by creating effective, efficient and transparent regulatory mechanisms to achieve faster medical product approvals and ensure their subsequent availability, especially for the treatment of neglected and priority diseases in various African markets (9,18,26,31). The AMRH initiative was created with the intention of increasing access to medical products through effective harmonisation of regulatory requirements and practice. This effective harmonisation among African NMRAs would enable them to meet internationally acceptable regulatory standards. In addition, the initiative intended to support AU Member States and regional initiatives that sought to align medicines regulation, fill in challenges faced in medical products regulatory capacity, as well as promote local pharmaceutical production and trade across African countries (3,10,13,15,16,18,19,21,30,37,40,49).

In addition to aiming to increase patient access to quality medicines, the AMRH initiative envisaged benefits such as optimised labelling requirements that enable the sharing of packaging across member states. This would potentially facilitate the supply and distribution of essential medical products across Africa as well as enable harmonised GMP standards and the sharing of GMP certificates as part of efforts to reduce duplicative inspections (37). As RECs predominantly work in isolation, the AMRH initiative adds value by providing the required coordination to prevent duplication of efforts and ensuring consistent approaches, especially since more than 75% of African countries belong to a minimum of two RECs (16,18). The AMRH initiative, in the short-term, intended to contribute to the standardisation and simplification of the medicine registration process to meet international standards and best practices (18). It is important to acknowledge the significance of these short-term targets and successes as they contribute to long-term policy change goals (13). In the medium term, the initiative aimed to provide a mutual recognition framework and a centralised medicines registration procedure among RECs and across Africa, therefore facilitating marketing authorisation decisions in the member states (18). In the long term, the desired outcomes are to have:

i. reductions in the time taken for medicines to reach African markets;
ii. improvements in access to quality-assured, safe and efficacious medical products for priority and neglected diseases;
iii. market increases for local pharmaceutical manufacturers; and
iv. improvements in treatment options and outcomes for patients in Africa (18).

As the initiative progresses, these systems will be built upon in the longer term with the intention of eliminating the need to engage every member state at every stage of the medicines registration procedure.

Regarding regulatory capacity, the AMRH initiative aims to increase the capacities of NMRAs and in particular, to strengthen the administrative, structural and technical aspects of regulation (19). This will assist the AU Member States to enhance and facilitate their decision making processes for the registration of medical products, and to exercise better control over the products in circulation (19). In the RECs, the continental AMRH initiative was being implemented with the aim of strengthening regulatory capacity, and advocating for the harmonisation of regulatory requirements, which also contributes to the end goal of expanding access to medical products for African patients who require them (13,16,37). Therefore, two indispensable elements of the AMRH initiative are the building of regulatory capacity and the facilitation of information exchange (19). In addition, the AMRH initiative aims to improve Africa's fragmented medical product registration and regulatory system by transitioning from a country-focused approach to a simplified collaborative regional approach (9,10). This transition begins with harmonising and streamlining technical requirements for the registration of medical products (9). Eventually, the AMRH initiative would gradually expand its scope of work from generic medicine registration to include performing other regulatory functions such as oversight of vaccine clinical trials, pharmacovigilance, and the registration of NCEs, medical devices and diagnostics (9,10,16). In order for the scope of work to be successfully expanded, the different partners and stakeholders need improved coordination as well as harmonisation to avoid

duplicative effort, fragmented priorities and ensure the optimum use of available resources (10). Furthermore, the AMRH initiative, from a regulators point of view, assists with functioning at an optimum level in a resource constrained environment (30). AMRH promotes the values of strengthening the capacities of NMRAs, promotes shared practices, and the joining of regulatory expertise (13). The strategy of the AMRH initiative is to develop regional regulatory platforms with harmonised standards (technical requirements/guidelines), information management systems, joint regional dossier assessments and GMP inspections, including work-sharing and streamlined decision-making processes (7,10,19,31). The strategic areas of focus for the AMRH initiative include:

- the reform and harmonisation of policy and regulatory frameworks;
- regulatory capacity development;
- improving communication and creating a conducive environment for regulatory harmonisation using monitoring systems;
- attaining sufficient regulatory control;
- mobilising political support and the requisite technical/financial resources; and
- knowledge management (8,13,20).

The AMRH initiative, recognising and respecting the sovereignty of AU member states, notes the importance of accountability by member states in order to ensure that the coordination of harmonisation activities proceed optimally (20).

The AMRH initiative sought donors and relevant stakeholders to offer support for its aims (18,30). There are several reasons that were outlined for investing in the AMRH initiative and key amongst them is that the initiative would offer AU Member States an opportunity to undergo regulatory systems strengthening and be in a better position to more effectively use its human and financial resources. Ultimately, investing in the AMRH initiative would also potentially create a more enabling environment for the attainment of health related developmental goals (17,18). The initiative emerged as the result of a joint venture of NEPAD, PAP, the AUC in collaboration with WHO, the World Bank, the Bill and Melinda Gates Foundation (BMGF), the Clinton Health Access Initiative (CHAI) and the United

Kingdom's Department For International Development (UKDFID) (3,7,10,15,16,18,26,30,31,37). This is a partnership that took into consideration each partner's niche area and was created to facilitate the AMRH initiative in terms of political advocacy, financial and technical resource mobilisation, and continental coordination (10,18). In 2011, a Global Medicines Regulatory Harmonisation Multi-Donor Trust Fund (GMRH-MDTF) was established, under the World Bank's fiduciary oversight, for the promotion of regulatory harmonisation, and for strengthening governance and regulatory systems (10,37). The GMRH-MDTF, initially funded by BMGF, enabled the pooling of funds from donors, the assurance of fiscal accountability, and ensured that the necessary resources needed by RECs are made available in a coordinated and flexible manner (10). DFID, US Government/PEPFAR, The GAVI Alliance (GAVI) and IFPMA are the other donors who either committed or contributed to the GMRH-MDTF (10).

The implementation of the AMRH initiative falls under the Pharmaceutical Manufacturing Plan for Africa (PMPA), which was endorsed in 2007 by the AU Conference of Ministers of Health in response to a call by the African Heads of State and Government in 2005 (5,9,13,16). In Africa, there have been ongoing regulatory harmonisation initiatives based on the decision of the AU Heads of State and Government on the PMPA and African Union Roadmap on Shared Responsibility and Global Solidarity for AIDS, Tuberculosis and Malaria Response in Africa, which gave the quality, safety, efficacy and affordability of medicines, including blood products, a high priority (3,47). Under the PMPA, the AMRH initiative received policy and political support which specifically recognised the need for AU Member States to engage in medicines regulatory systems strengthening activities by pooling their resources in order to attain public health policy priorities (10,16). These regulatory systems are important to assure the quality, safety and efficacy of medical products that are locally manufactured, in addition to contributing positively to public health (16). The establishment of the AMRH initiative, which contributes to the realisation of the PMPA vision, is also part of a mitigation strategy for capacity limitation impediments that a major number of NMRAs in Africa grapple with when

executing basic regulatory functions (3,13,21,47). In April 2007, the AU Conference of African Ministers of Health (CAMH3) under the theme "Strengthening of Health Systems for Equity and Development in Africa" responded to the AU Assembly decision {Assembly/AU/Dec.55 (IV)} which was taken in January 2005, at the Abuja Summit, to develop the PMPA within the NEPAD framework (1,3,6,8,13,31,36,48,49). Having a viable pharmaceutical industry in Africa will positively impact the health systems on the continent, strengthen economic autonomy, and contribute to sustainable socioeconomic development (8,13). However, trade in pharmaceuticals is currently being hindered by poorly harmonised administrative and technical medicines registration requirements (16). This creates technical barriers to the free movement of locally produced and imported products, and negatively impacts timely access to essential medical products for patients (16). For local pharmaceutical production to be successful, it will be partly dependent on creating viable market sizes through intra-regional and intra-continental trade (16).

The PMPA outlines a regional strategy to pool the skills and investments of countries, enabling them to determine as well as manage research, manufacturing, medicine access, and innovation (8,31,47). The aim of the PMPA, which identified the creation of an enabling regulatory environment to be a priority that needs addressing, is to ensure that African countries are able to provide all their citizens with quality-assured, safe and efficacious essential medicines as part of their national obligations, in addition to the realisation of both direct and indirect economic growth (3,8,13,31,36,47–49). The objective of the PMPA, broadly speaking, is to improve the quality of medical products even in countries that are neither involved in local pharmaceutical production nor have a desire to be (8). Within the framework of the PMPA, the AMRH initiative has been implemented over the last ten years by the NPCA, in collaboration with WHO and partners, with the intention to support the strengthening of medical products regulatory systems in RECs and Member States (3,13,16,21,47,50). The partnership has resulted in RECs and RHOs, which have been supported to serve as regional information sharing platforms, benefitting from harmonised regulatory

requirements, standards, systems, legislation and practices (3,21,26). The intention of the work done by RECs is to be a stepping stone for the harmonisation of activities in Africa (3). Medicines regulatory systems harmonisation is a pivotal aspect when laying the foundation for establishing the African Medicines Agency (3,13,14,23,47,58). Moreover, strengthening and harmonising regulatory systems in Africa will help in improving the predictability and efficiency of marketing authorisation approvals, with the goal being to improve timely access and delivery of health technologies for patients who most need them (14).

Within the African regulatory landscape, there has been a general development geared towards ensuring that medical products are available to the populations that require them (53). As a result, the AMRH initiative has expedited the approval process for medical products and assured industry of access to expanded regional markets (21). Currently, medical product approvals at the national level are proceeding faster as a result of countries engaging in joint assessments (21). Although they are at different maturity levels, countries in Africa have also established regulatory systems that have gradually worked to protect and promote public health (53). However, regulatory systems in certain territories are, to some extent, increasingly become a barrier for patients to access medicines in a timely manner (53). Regulatory barriers have also been on the rise over the last decades resulting in delays in approvals and increased costs (21). To address some challenges encountered in regulation, the AMRH initiative has harmonised medicines regulatory systems and successfully demonstrated the possibilities of coordinating regulatory harmonisation at a continental level (3). In addition, the AMRH initiative could result in market defragmentation at the sub-regional level (8). In order to harness this potential economic market, there needs to be market defragmentation for the pharmaceutical manufacturing business to be viable on the continent (3,8). As Africa is invigorating the 1991 Abuja Treaty for the African Economic Community's establishment, the continent needs to leverage existing harmonisation and integration opportunities through strengthening and fast tracking these processes (13). The policy to implementation gap that has been an impediment to medicines registration advancement efforts is therefore being resolved by the AMRH initiative which is suitably positioned to bridge the gap

(16). The AU, RECs and partners are leveraging lessons learned from past experiences of harmonisation models and schemes around the globe, such as those within ICH, Europe, America and Asia, to assist Africa attain a harmonisation process that is efficient (37). Furthermore, the Eighteenth Ordinary Session of the Heads of State and Government Orientation Committee (29-30 January 2012) Decision Assembly/AU/Dec.413 (XVIII) Para 6 endorsed the AMRH initiative implemented through RECs (49). It was decided that the AMRH initiative shall serve as the foundation for the establishment of the African Medicines Agency (AMA) (1,3,10,11,13,37,49,58). The AMA is therefore expected to become the continent's focus of regulatory standards harmonisation, process optimisation, and resource coordination across the continent (11).

3.4.2 Harmonisation in the Regional Economic Communities

Africa has witnessed progressive growth in the regulatory environment and the AMRH initiative has been at the centre of this growth (37). The AMRH initiative launched regional medicines regulatory harmonisation (MRH) projects, by leveraging the continental reach of NEPAD Agency and the technical lead role of WHO, that have been instrumental in assisting NMRAs in Africa to determine priority action areas for regulatory systems strengthening and harmonisation (10). Prior to launching regional MRH projects, the AMRH initiative partners carried out a situational analysis of the regulatory status of medical products in the EAC, SADC and ECOWAS regions (10). In the EAC, the assessment showed variations in laws and regulations of the countries, a lack of mutually recognised legal frameworks and significant differences in the region's NMRA capacities (10). The assessments carried out in SADC and ECOWAS showed similar results with the member states of the respective regions having variably comprehensive legal frameworks which then affects their capacity to effectively regulate their markets (10).

Owning and driving the AMRH initiative, African countries and RECs created MRH project proposals which allowed them to tailor the objectives and activities of the projects to suit their specific needs, contexts and preferences (16). However, these objective and activities needed to be in line with the objectives

of the continental AMRH initiative (16). There have been collaborative efforts in and between RECs such as the EAC, ECOWAS, WAEMU and SADC following the launch of the MRH programmes and their subsequent implementation (21,49). Other RECs and ROs such as ECCAS, the Organization for Coordination in the Fight Against Endemic Diseases in Central Africa (OCEAC), and the North-Eastern regional collaboration and harmonisation led by the Intergovernmental Authority on Development (IGAD) have also recorded successes through their ongoing cooperation efforts (49). A number of these RECs have supported medicines registration harmonisation by creating common pharmaceutical policies and operational plans backed by high-level political commitments and mandates (16,18). Generally, these MRH projects have reported differing progress to date (31), and decisions regarding registration will continue to be firmly that of sovereign nations (16).

Collaboration between WHO and relevant stakeholders, including the research-based pharmaceutical industry, on collaborative registration procedures that support fast and efficient review and approval of essential medicines in Africa is essential (37). Africa, with its fragmented and weak markets, needs to engage in the strengthening of its legal system and consolidation of its management structures and processes (13). With WHO involvement, harmonisation discussions then moved to a global platform which facilitated dialogue and the exchange of lessons among regulators from different regions with different capacities (13). In order to achieve access to quality-assured, safe and efficacious medical products for the public, regional medicines harmonisation needs concerted efforts and consolidation (26). The AMRH initiative has made significant progress in this regard and has mobilised technical and financial resources in order to advance the harmonisation of pharmaceutical regulations in Africa (31).

3.4.2.1 The EAC's Medicines Regulatory Harmonisation Initiative

Under the AUDA-NEPAD, regional MRH activities started with the EAC as it was selected as the first region to begin the implementation of its harmonisation plans (3,7,10,31,37,40). The EAC consists of Burundi, Kenya, Rwanda, South

Sudan, Tanzania, and Uganda (5,7,11,52). The original thinking was to pilot the AMRH initiative in one REC, the EAC, for learning purposes and then have a gradual geographical expansion of the AMRH initiative until it covered all countries in Africa (9–11,53). In line with the foregoing, the EAC MRH initiative was officially launched on 30 March 2012 in Arusha, Tanzania with the goal of improving its citizen's access to quality-assured, safe and efficacious essential medical products for the treatment of conditions that have public health importance (3,5,7,10,11,20,52,53). When the initiative was launched, only Tanzania, Uganda, Kenya, Burundi, and Rwanda were involved (10,20,31) and the project was intended as a five year pilot of the broader AMRH initiative (5). Although this chapter is on regulatory harmonisation in Africa's regional economic communities, more attention is being paid to the EAC's MRH initiative because of its importance. The EAC's initiative:

i. Had the burden of producing results from the pilot which would be used for the determination of whether or not it would be feasible for other regional blocs to begin their own harmonisation and optimisation programmes, and more importantly, if it was worthwhile to pursue a continent-wide initiative (5);
ii. Offers lessons that are critical for scaling up this model of regulatory harmonisation that other African RECs can use following its piloting of harmonised guidelines for medical products registration and GMP, Quality Management Systems (QMS) and Information Management Systems (IMS) (9,53);
iii. Serves as the starting point for the expansion of the AMRH initiative into other RECs (7,10,11,13) as it is the first successful regional group of the AMRH initiative (20) and it has made significant progress to date (31); and
iv. Assists in the provision of an engine for the development of the African Medicines Agency (11).

It is anticipated that the African Medicines Agency will build on the successes of the EAC's MRH initiative in order to advance regulatory harmonisation across

the continent (11). The success of the EAC's MRH initiative therefore has an influence on the success of forthcoming initiatives, especially at a time when Africa is working towards an African Medicines Agency (7,20). As regulatory harmonisation efforts in Africa proceed with the aim of establishing a single continental agency, the EAC will also continue to be the benchmark for the other African RECs (53).

3.4.2.1.1 The History of the EAC's Medicines Regulatory Harmonisation Initiative

In 2000, through the Research, Policy and Health Systems Working Group, the EAC Council of Ministers gave the EAC Secretariat the task of drafting a common medicines policy, harmonised regulations and procedures (5,53). The result of this policy was the 2005 recommendation for the promotion of regulatory harmonisation via existing RECs, which included the EAC, by the African Drug Regulators Conference. This was followed by the creation of five Technical Working Groups (TWGs) in 2006 on Administration, Quality, GMP, Safety and Efficacy, and Veterinary Medicines (53). With WHO providing technical support through a Memorandum of Understanding (MoU) with the EAC, these TWGs agreed to revitalise their commitments to supporting the proposals for funding that then led to the EAC MRH project being launched (53). The activities of the EAC Member States were organised around TWGs because the EAC Secretariat was restricted to activity coordination while NMRAs were the entities equipped to give the required technical input (53). In addition, by having NMRAs working together on guideline creation, there began to be diffusion of expertise across the EAC and the bridging of gaps that existed between the NMRAs (53).

The planning for continent wide medicines regulatory harmonisation started in earnest in 2009 (5). In February of that year, a meeting was co-hosted by the AUDA-NEPAD and PAP, and at this meeting objectives of a consortium dedicated to attaining an AMRH initiative were endorsed by policymakers and regulators from close to 40 African countries (5). To achieve this vision, the consortium began working through RECs. However, there were insufficient

funds and only one pilot project could be supported (5). The consortium therefore decided to solicit proposals from each REC and the most promising regional MRH plan would be funded for five years (5). Consultants were then engaged by AUDA-NEPAD in 2010 to conduct in-depth evaluations of the regulatory capacity and scope of activities of each EAC Member State (5). In 2011, the World Bank started providing the EAC harmonisation initiative with funding (20) and in 2012 the EAC was selected as the REC to pilot the initiative, receiving US$5.5 million (5). The initiative was then launched by AUDA-NEPAD and the EAC, in collaboration with AMRH initiative partners, anchored on the existent EAC regional cooperation on health under Chapter 21 Article 118 of the EAC's Treaty on Health (7,16,53).

At that time the EAC accounted for 14% of the African population and South Sudan was not yet a member state (5). Unlike the other African RECs, the EAC is made up of a small number of member states with most of them sharing a common history, language, culture as well as infrastructure, which all enabled cooperation (5). A customs union and common market were already in force in the region at the time of the region's application, and a monetary union was planned for 2024. In addition, the EAC had future plans for a political federation which would make the REC a "super state" (5). Furthermore, a political platform for medicine regulatory harmonisation was provided by the previously mentioned Chapter 21, Article 118 of the Treaty for the Establishment of the EAC (5). The treaty provides for harmonised medical product registration and regulation with the aim of attaining good control of pharmaceutical standards without negatively impacting the movement of medical products within the EAC region (7,16,53), and calls for the development of "a common drug policy which would include establishing quality control capacities and good procurement practices" (5). Lastly, the NMRA staff of Kenya, Tanzania and Uganda had prior experience working with each other and with WHO staff during a pilot project in which medicine registration applications to NMRAs and WHO's prequalification programme were jointly assessed (5).

In spite of these advantages highlighted above, the EAC faced a considerable challenge in developing a regional regulatory system in one of Africa's fastest growing RECs (5). The system needed to work for approximately 150 million people, scattered across an estimated 2 million square kilometres, in five short years (5). Additionally, the system had to contend with the fact that all EAC Member States, with the exception of Kenya, were low income countries as classified by the World Bank (5). The health systems of the EAC Member States were also grappling with their own challenges e.g. the life expectancy across the region was lower than the global average (5). Moreover, the EAC's initiative was expected to identify a sustainable funding mechanism that would allow it to expand its regulatory functions after the initial five year catalytic support expired (52). However, progress in this area has not been as desired. Initially, the plan was for the EAC Member States to fund a portion of the initiative's activities beginning several years after the start of the project and this funding never materialised (52). The EAC was also aware when it crafted its MRH project that it could not simply replicate the structure of existing regional regulatory bodies that had developed over years; instead, it had to develop a structure that would result in the region immediately accruing benefits while taking into consideration the EAC's political and economic realities (11). Therefore, the EAC MRH project relies on decisions from joint assessments made by the member states' NMRAs rather than relying on a single EAC NMRA (11).

3.4.2.1.2 The Goals of the EAC's Medicines Regulatory Harmonisation Initiative

The EAC, through region-wide collaboration, aimed to increase the number of quality medicines it registered by making the application process simpler for manufacturers and secondly, to increase the speed of application review without any decrease in rigour by modernising the assessment processes (5,52). In addition, the initiative sought to implement harmonised technical requirements, IMS and QMS in each of the EAC Member States as well as to build capacity for the implementation of the MRH project (7,10,31,53). Another goal of the initiative was to have a legally binding mutual recognition framework so as to have EAC countries recognising the regulatory decisions of each other (52).

Despite the EAC's Council of Health Ministers signing a Cooperation Framework in May 2018 which includes a non-binding agreement by the member states to base their regulatory decisions on joint activity outcomes (52,80), to date there is no formal mutual recognition framework (52). The only mutual recognition agreement that exists in the region is the one of Zanzibar's NMRA unilaterally recognising the regulatory decisions of mainland Tanzania's NMRA (52,80). As an intermediary step toward the region having legally binding mutual recognition agreements between all its member states, the initiative intends to pursue unilateral recognition agreements such as the one of Zanzibar and Tanzania's NMRAs as well as bilateral agreements (80). Furthermore, the project aimed to achieve optimum resource use by having processes that enable regulatory information sharing, joint activities and the use of risk-based approaches (53). By optimally using the resources available, EAC NMRAs are able to progressively allocate the resources at their disposal in the best and most value adding activities (53).

The EAC MRH initiative, to attain its overarching goal of improving access to quality medical products, made the decision to focus on:

- Developing and implementing:

i. A common technical document that manufacturers could use for medicine registrations within any EAC Member State;

ii. A common information management system for the registration of medical products that would link all member states, as well as to the EAC Secretariat;

iii. A quality management system in each NMRA to ensure that each member state performed regulatory activities in a manner that is uniform and rigorous;

- Building regional and national capacity to implement registration processes as well as harmonise and align technical standards; and
- Developing and implementing a mutual recognition framework for member states to eventually recognise their neighbours' regulatory findings and decisions (5,52).

3.4.2.1.3 The Structure of the EAC's Medicines Regulatory Harmonisation Initiative

Most regional bodies that exist rely on a central authority to perform regulatory functions and a legal framework that binds member states to that central authority's decisions (5). However, it was not possible for the EAC to do this in the five years of the pilot. Instead, the region opted to implement a new decentralised regional regulatory system that would function well, be quick to establish, and have each member state taking primary responsibility for a different regulatory function (5,11). This approach enables specialisation and ensures the active involvement of every NMRA while optimally using the limited regulatory expertise available in the region (5,11). The final decision regarding marketing authorisation would continue to be at the discretion of the NMRAs even though the EAC Member States had harmonised technical requirements and performed joint assessments/inspections (5). The willingness of EAC Member States to rely on joint assessment decisions is based on trust and goodwill rather than legal requirements (5,11,72). To assist in carrying out its functions, the EAC MRH project relied on a Steering Committee, TWGs, and a Project Coordination team (5). The Steering Committee was composed of Heads of EAC NMRAs, chief pharmacists, the EAC Secretariat, and AMRH initiative partners (5). Meetings were held twice a year by this committee to approve work plans and budgets, as well as to review and endorse guidelines (5). In addition, TWGs were capitalised on as they are a model which was already being used by the EAC successfully (5). Leadership roles were assigned for the initiative based on each NMRA's strengths:

- Tanzania would lead the Medicines Evaluation and Registration Working Group as it had the most developed semi-autonomous NMRA;
- Uganda would lead the GMP Inspections Working Group;
- Rwanda would lead the Information Management Systems Working Group; and
- Kenya would lead the Quality Management Systems Working Group (5).

Two representatives from each EAC Member State made up the working groups, as well as staff from the EAC Secretariat, AUDA-NEPAD, WHO, and development partners (5). The TWGs would meet at least twice a year to draft technical guidelines and procedures which would then be presented to the Steering Committee for review and to be endorsed (5). In addition, a Project Coordination team had the responsibility of overall project planning, preparation, procurement, execution, monitoring, evaluation, and reporting. This coordination team was made up of a project coordinator, a health and informatics officer, an accountant, a pharmaceutical program assistant, and six focal staff drawn from each NMRA (5). This regional initiative also designed a twinning system for capacity building. EAC Member States with less mature regulatory systems were paired with more established NMRAs i.e. Zanzibar's NMRA was paired with Kenya's; Burundi's with Tanzania's; and Rwanda's with Uganda's (5,52). "Health cooperation and friendly competition" between NMRAs enables high quality and consistent assessments, as well as ensures that assessors are continuously upskilled (72). This arrangement allowed more mature NMRAs to pass on best practices, expertise and institutional knowledge as NMRAs worked together on joint activities such as product evaluations and GMP inspections (5,52). Additionally, the twinned NMRAs had the opportunity to build relationships and confidence to enable staff to comfortably communicate with each other, even outside the framework of joint activities (5). Staff exchanges were also set up to strengthen these twinning relations and to allow for learning from the operations and standard operating procedures of other regulatory authorities, as well as how to undertake scientific reviews and regulatory activities (5,52). Figure 1 shows the governance structure of the EAC's medicines regulatory harmonisation initiative.

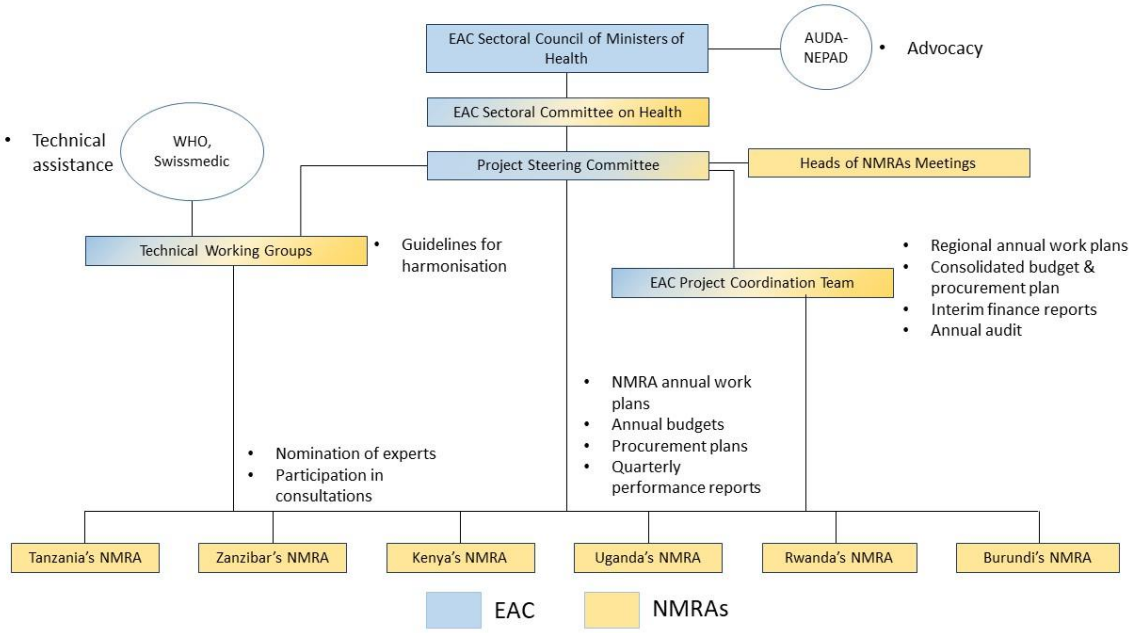

Figure 1: The Governance Structure of the EAC's Medicines Regulatory Harmonisation Initiative (5).

Important roles were assigned by the EAC MRH project to external partners as follows:

- The World Bank oversaw the project's finances, disbursing funds from the AMRH initiative's multi-donor trust fund to the EAC Secretariat who have the management of regional project funds as one of their roles;
- WHO and Swissmedic provided technical support to the EAC Secretariat and member states' NMRAs, as well as trainings on adhering to current international quality assessment standards and GMP inspections; and
- AUDA-NEPAD assisted in the coordination of the various stakeholders involved in the project (5).

The role of external partners in the EAC's MRH initiative is illustrated in Figure 2 below.

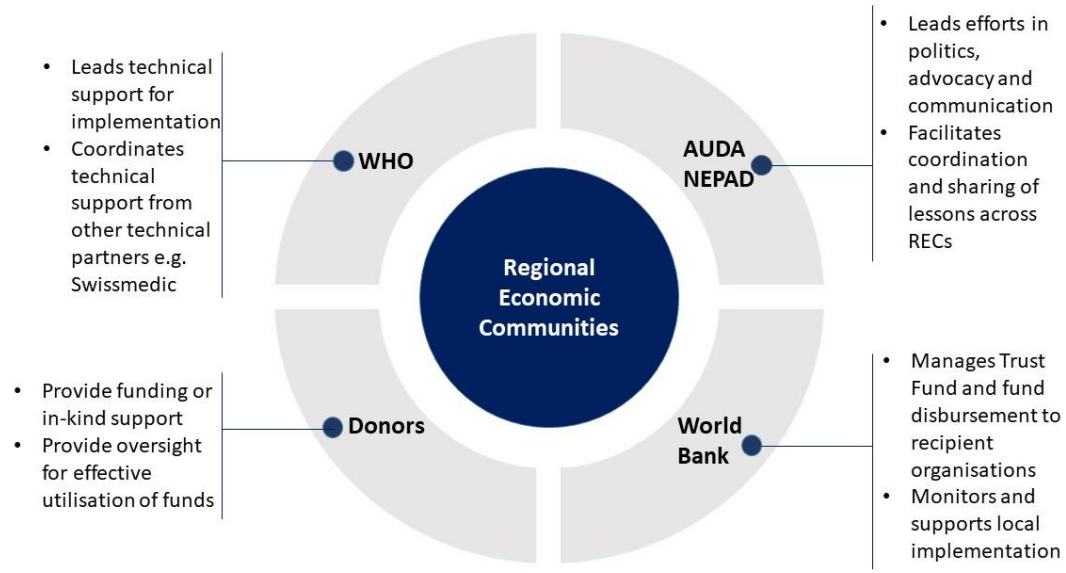

Figure 2: The Role of External Partners in the EAC's Medicines Regulatory Harmonisation Initiative (5). AUDA-NEPAD, African Union Development Agency-New Partnership for Africa's Development; Swissmedic, Swiss Agency for Therapeutic Products; WHO, World Health Organization.

3.4.2.1.4 The successes and shortcomings of the EAC Medicines Regulatory Harmonisation Initiative

In September 2014, the initiative finalised and approved harmonised registration guidelines, the CTD, GMP and QMS compendia (31). In January 2015, the CTD as well as the harmonised registration and GMP guidelines were launched, and the first joint assessment of dossier applications occurred in October 2015 (7). These harmonised guidelines have been used for a number of national registrations and EAC joint dossier assessments since their launch in January 2015 (31). The initiative also managed to successfully:

i. Increase the efficiency of assessing medicine registration applications (52);
ii. Pilot a process that has halved the average time it takes for NMRAs to conduct new medicine registrations (11)

iii. Enable EAC Member States that did not assess product dossiers for registration prior to the initiative to set up their own marketing authorisation systems;

iv. Adopt a modified version of the ICH's CTD so that manufacturers could use this CTD to apply for medicine registration in any of the EAC Member States;

v. Conduct joint regulatory activities which have resulted in the recommendation of medical products for registration by EAC Member States;

vi. Have a target timeline of 3 months or less in individual NMRAs for products that have been recommended for registration through the joint assessment process;

vii. Establish guidelines and SOPs, based on WHO guidelines, for both national and joint inspections of manufacturing sites in the region. This was done through the initiative's GMP Inspections Working Group which is led by the Ugandan NMRA;

viii. Reduce the number of assessments and inspections that manufacturers seeking to register a medical product using the region's joint process undergo;

ix. Build capacity and trust between the NMRAs acting as assessors or inspectors;

x. Build confidence in the resultant findings due to joint assessments and inspections being more transparent and stringent when compared to national assessments or inspections (52);

xi. Invite manufacturers of certain types of medical products that are not eligible for the WHO-PQP to apply for marketing authorisation through the joint assessment procedure, which inevitably attracted a high number of applications for these medical products e.g. anticancer and antihypertensive medicines;

xii. Draft harmonised pharmacovigilance guidelines, a pharmacovigilance roadmap and a business plan to guide activities in this regulatory function. This was done under the guidance of the working group led by Kenya;

xiii. Have the EAC Harmonised Compendium of Guidelines for Pharmacovigilance approved in March 2019 by the EAC Sectoral Council of Ministers;

xiv. Increase regulatory capacity in NMRAs across the EAC region;

xv. Have a functioning Information Management System in all EAC Member States which has increased NMRA efficiency and strengthened linkages across department (52);

xvi. Establish full-fledged NMRAs in Rwanda, South Sudan and Zanzibar (11,52); and

xvii. Oversee trainings that focus on regulatory capacity development in various functions. These trainings, conducted by WHO and Swissmedic, focused on, among other things, medicines evaluation and registration, GMP, QMS, IMS, and pharmacovigilance (52).

The EAC MRH initiative has been viewed by stakeholders and partners as being beneficial not only to NMRAs, but also to industry (53). The pharmaceutical industry welcomed this project which has improved the availability of medical products and contributed to a clearly defined and predictable system that is aligned with international best practice, e.g. the use of the CTD format (53). There has also been a reduction in SF medical products in the private market at both country and regional level due to external support for regulatory systems strengthening (75). By strengthening the regulatory landscape in the EAC region, there is increased local NMRA capacity in the region as well as a reduction in the gaps that exist between the various NMRAs (53). This capacity building is viewed to contribute significantly to the reduction in the learning curve particularly amongst the less mature NMRAs (53). The REC also adopted the AU Model Law on Medical Products Regulation in 2016 with the expectation that it would lead to the accelerated regulation of the quality, safety and efficacy of medical products in EAC Member States (31). Furthermore, the EAC region gained membership to the ICH Global Cooperation Group, allowing the region to attend meetings and be exposed to knowledge sharing with other non-African medicines regulatory harmonisation initiatives (20).

The EAC's MRH initiative has reported some challenges that it has faced and continues to grapple with, including:

i. A lack of transparency regarding the initiative's timelines, resulting in challenges for applicants who want to track the progress of their applications (52);
ii. A lack of easily accessible public information about the process (52,80);
iii. Inadequate follow up by the NMRAs to the questions of applicants, and vice versa (52,80);
iv. Failure of assessors to scrutinise applications for errors or omissions early in the process, resulting in avoidable queries later on;
v. Lack of trust between NMRAs stemming from the different capacities of the NMRAs as some regulatory authorities are mature whereas others started registering medicines as recently as 2016. However, even mature NMRAs can refuse to fully rely on each other's decisions (52,72);
vi. Lack of interoperable systems to link IMS platforms of EAC Member States to each other, and to the EAC Secretariat (52);
vii. Lack of a legal framework that is binding on the EAC Member States to recognise the regulatory decisions of their neighbours (52,72);
viii. High staff turnover and understaffing, including in key leadership roles and at the technical staff level e.g. since the initiative began, Burundi has trained 4 pharmacists to partake in product assessments and all of them are no longer employed by the NMRA as they have gone to other missions, ministerial departments, international non-governmental organisations, or the private sector (52);
ix. Poor communication with the initiative's technical partners regarding joint assessment scheduling, making it difficult for the partners to effectively provide support (52);
x. Delays in receiving national marketing authorisation once a joint recommendation has been made (52,72,80); and
xi. A belief that activities associated with the initiative are "extra" duties as well as many EAC MRH initiative participants believing that NMRAs, in

particular the Heads of NMRAs, have not fully taken up the leadership mantle (52).

3.4.2.1.5 The EAC's Future Plans for its Regulatory Harmonisation Initiative

Going forward, the region intends to establish a Cooperation Framework Agreement among its member states in order for joint assessment and inspection decisions to be honoured region-wide (80). In addition, the initiative hopes to establish a semi-autonomous regional regulatory body, the EAC Medicines Agency, by 2022 which will have dedicated staff to conduct joint regulatory activities, as well as promote a legal framework for reliance on and recognition of joint assessment recommendations by EAC Member States (11,80). The region also intends to strengthen and optimise the regulatory activities it has been performing since the initiative began while broadening the scope of its initiative to include new types of medical products, e.g. invitro diagnostics (IVDs), vaccines, biologics and biosimilars, and medical devices, as well as broadening its scope of regulatory functions e.g. to include clinical trials oversight, post marketing safety and quality surveillance (11,52,80). The intended focus is mainly on medical products that are ineligible for the WHO-PQP (80). The WHO-PQP was primarily established for the evaluation and subsequent recommendation of products that meet WHO's standards of quality and efficacy to UN procurement agencies and global health procurement organisations e.g. the Global Fund, UNICEF, and GAVI (80). Another area of focus will continue to be NMRA capacity building as the initiative aims to design an IMS that links all of the NMRAs in the EAC as well as work with WHO and other SRAs to continue with the development of its staff's expertise in the field of regulatory science (80).

3.4.3 The Perspective of the Pharmaceutical Industry

Over the last decade, pharmaceutical companies worldwide have continued to rationalise manufacturing sites as a cost reduction strategy (39). This has created a scenario whereby medicines are supplied from centres of excellence scattered across the world (39). Country specific requirements, which an increasing number of African countries are using, are a barrier to market access and country

specific labelling requirements, which include scheduling status and registration numbers printed on the medical product's packaging, do not support harmonisation principles (30,39). The pharmaceutical companies that operate in Africa are also reluctant to export their medical products to certain countries in Africa (20). These pharmaceutical companies experience difficulties in complying with the technical requirements of the different countries, as well as registration, retention and inspection costs (17,20). The use of country specific labelling requirements increases medical product costs to specific markets in Africa and in some instances, pharmaceutical companies may opt to not supply medical products to these countries (17,39). Additionally, the country specific labelling requirements have problematic implementation (17,39).

The absence of harmonised technical requirements in many African countries and the lack of regulatory capacity impedes timely access to essential products (16,30). Narsai conducted a study in 2010 which reported that registration timelines are variable and inconsistent, with only approximately half of medical products being registered in two years (39). Having registration timelines that are predictable and efficient promotes access to medical products and serves as an incentive for more pharmaceutical companies to register their innovative products in African markets (39). In resource constrained countries, the recognition of international standards is of paramount importance (39). By using international standards, pharmaceutical companies are better able to comply with regulatory requirements and from the viewpoint of the NMRA, it ensures the maintenance of high standards, alignment with international best practice and optimally functioning in an environment with resource constraints (39). Some respondents in the study done by Narsai indicated that there is some alignment with international standards whereas others stated that international standards were not recognised (39). As part of the process of harmonisation, the registration status of medicines in territories with benchmark NMRAs should be recognised (39). However, African countries must do so while still maintaining their sovereignty in regulatory decision making (39). The scenario suggested as being the most ideal would be (i) to have international standards being recognised, (ii)

African countries maintaining their sovereignty, and (iii) these preceding points occurring without increasing the complexity of medical product registration (39).

According to Narsai (2010), 85.7% of the study respondents stated that they had endured an experience of being unable to supply medicines into African markets due to reasons which are all related to the regulatory requirements for the registration of medicines (39). Delays in the approval of post-registration amendments to registration dossiers are also a reason for supply interruptions (17). Pharmaceutical companies have discontinued supply of between one and five medical products to African countries for regulatory reasons such as registration, renewal and GMP inspection fees (17,30). Failure to comply with regulatory requirements, such as country specific labelling on the medicine's out pack not having the country's registration details printed on it, has resulted in medicines being indefinitely held at customs (39). There is a clear link between the considerably high levels of interrupted supply and the regulatory requirements (17,39). Unless country specific requirements are revised and international standards are recognised, the absence of alignment with international standards, the prevalence of SF medical products, GMP inspections, and unpredictable approval timelines will all continue to negatively impact product supply (39). Furthermore, pharmaceutical companies have indicated that SF medical products are prevalent and problematic in certain African markets (17). Some pharmaceutical companies are also of the opinion that having stringent regulatory requirements will curb the prevalence of SF medical products in circulation within these markets (39).

The majority of pharmaceutical companies operating in African countries view GMP inspections, an important source of income for most countries, as a barrier to medical product/health technology registration and subsequent supply (17,39). A number of pharmaceutical companies have indicated that GMP inspection fees in certain African countries are too high and follow-up inspection costs are also too high relative to the required inspection frequency (17,39). In the majority of African countries, the markets are small to warrant charging the same fees that are charged in big markets (13). The recognition of the international GMP status

of manufacturing sites is a crucial consideration for African regulatory harmonisation (39). The impact of increasing the number and frequency of GMP inspections is approval delays, and interrupted sterile manufacture and medical product supply as certain manufacturing sites shutdown during GMP inspections (17,39). GMP inspection costs could also be a deciding factor in whether pharmaceutical companies pursue medical product/health technology registration in a country (17,39). For pharmaceutical companies, GMP inspection requirements, GMP inspection fees and country specific labelling requirements are problematic (17,30).

National and regional medicines registration is a means of ensuring the quality, safety and efficacy of medical products being provided to the public. However, medicines registration requires applicants to provide a lot of information (26). Manufacturers are met with myriad disparate regulations, frequent delays and minimal process transparency (16). Applicants may fail to comply with the process of medicines registration as the costs involved may outweigh the benefits (26). Consequently, there is inadequate medicines availability in many African countries as manufacturers do not yield benefits from the economies of scale associated with faster access to larger markets, and there is slow introduction of competition and delayed cross-country pooled procurement (16). Furthermore, pharmaceutical companies experience varying registration timelines, and they are generally between one and three years (17). There is a need to carefully scrutinise the current regulatory requirements to determine whether they are value-adding or not in terms of the medicines registration process (17). In this way, the current processes for product registration can be streamlined to shorten the overall medical product registration timelines (17). Moreover, consolidated manufacturing and internal supply chain arrangements within pharmaceutical companies are increasing the level of complexity (17). Having to manage internal and regulatory compliance requirements is causing pharmaceutical companies to decide not to supply medical products to certain markets in Africa (17,20). At the country level, there appears to be a disconnect between AMRH initiative objectives and the experiences of pharmaceutical companies (17). Regulatory burdens being faced by pharmaceutical companies must be addressed to alleviate

their plight and to positively contribute to the attainment of the objectives of the AMRH initiative (17).

82% of respondents in the study conducted by Narsai (2010) are positive about the AMRH initiative and emphasised the need to focus on implementation as prior attempts at harmonisation did not come to fruition as a result of the lack of political will and commitment to implementation (17,39). In order for the AMRH initiative's objectives to be met, key industrial stakeholders need to be consulted and give their input (39). Pharmaceutical companies that operate in these markets can give key insights from a practical perspective (39). Successfully implementing the AMRH initiative will result in gains for all key stakeholders in the medicines value chain, including positively impacting the health status of populations in Africa (17,39). In a more recent publication by Dansie *et al.* (2019) on regulatory harmonisation in the EAC region, most pharmaceutical companies are supportive of medicines regulatory harmonisation efforts and are appreciative of the possibility of joint assessments (7). A different study by Calder (2016) supports the sentiments expressed in the EAC region and reports 82% of pharmaceutical company representatives being in support of the harmonisation of legislative frameworks for the regulation of medical products (20). The pharmaceutical industry deems it easier to submit one dossier application to various countries and this is considered welcome progress to ensure greater market access (7,20). A number of respondents from the Dansie *et al.* publication indicated that they had submitted joint dossier evaluation applications not only to gain quicker market access, but to support the regional initiative (7). However, concerns were raised by manufacturers who primarily serve the local market about the impact of harmonisation on their competitiveness as many of the manufacturers based in the EAC region produce a similar product portfolio (7). The pharmaceutical industry also had an expectation that these processes would be self-executing, i.e. joint evaluation decisions would be automatically accepted by NMRAs, and receipt of marketing authorisation and GMP certification would be faster (7). In addition, the pharmaceutical industry representatives of the EAC region have expressed their desire for a robust, predictable, transparent and accountable centralised decision-making EAC agency for jointly evaluated

products which handles all documents and payments related to their respective applications (7,80). These representatives also have a desire to pay higher marketing authorisation fees in order to fund a centralised system that has an optimised process for product assessments and GMP inspections in the region. This demonstrates that such a system, once fully operational, could become self-sustaining through levying regional coordination fees for the joint activities (80). Furthermore, Dansie *et al.* found that pharmaceutical companies perceive the implementation of the harmonisation efforts to not be fast enough, which makes it difficult to attain the envisioned harmonisation benefits. Moreover, there is limited knowledge and awareness about the harmonisation efforts as well as the MRH project's scope, direction and goals (7). Despite these responses from industry, they do acknowledge that the EAC MRH project has brought about several improvements in the REC, for instance regulatory capacity has been strengthened particularly in countries with weak capacity (7). The limitations of the Dansie *et al.*'s study are that they performed a numerically small number of interviews; they did, however, encompass most companies that participate in the EAC joint assessment. Secondly, the authors focused only on the EAC joint assessment procedure and the EAC joint GMP inspections which then excluded obtaining progress and industry's perceptions related to the EAC MRH's other goals.

For the most part, research in the public health field has ignored industrialisation as a social determinant of health and the public health research that has included industrialisation has merely labelled it as one of other relevant input sectors (75). However, researchers, policy makers and industrialists in Africa are increasingly investigating and advocating for synergies between local pharmaceutical production and improvements in healthcare quality and coverage, particularly for low-income populations (75). There is an evident paradigm shift from considering industrial and health sector developments as being in competition, to perceiving symbiosis (75). In addition, NMRAs need to consider the following key principles:

i. the risk of over-regulation and the impact that has on medicine access and public health;
ii. adopting systems used by benchmark agencies in a resource constrained environment; and
iii. the approval status of medical products/health technologies by benchmark agencies in order to optimise regulatory approval processes (17,39).

The studies highlighted in this section all point towards both national and international pharmaceutical manufacturers having significant goodwill towards efforts in medicines regulatory harmonisation being a success (7). However, additional barriers such as political instability and logistical problems involving wholesalers/distributors need to be addressed in order for certain markets in Africa to become attractive to pharmaceutical companies and for the cost savings of MRH to become a reality (7). Therefore, it is important to take a collaborative approach to harmonisation and involve the pharmaceutical industry. The NMRAs and the pharmaceutical industry should work together for the attainment of common goals, including for the simplification of intra-regional export (20,75).

3.4.4 The Potential Benefits of Medicines Regulatory Harmonisation in Africa

There are many potential advantages offered by medicines regulatory harmonisation to low-income countries (7). In Africa, regulatory harmonisation offers several benefits to the various pharmaceutical stakeholders, including patients and industry (17,34,37–39). This makes the harmonisation of technical requirements for medicines regulation desirable for several reasons including public health protection (19,37). The primary aims of harmonising technical requirements and procedures for the registration of medical products are (i) to improve public health by increasing the timely access to quality-assured, safe and efficacious treatments for priority diseases (16), and (ii) to reduce registration cycle times for medical products, including the lead-time associated with meeting the requirements of different countries, starting with generics and expanding in scope to include other medical product categories such as NCEs, vaccines,

diagnostics, as well as other regulatory functions, such as CT and safety surveillance (10,18). By reducing the time taken for the registration of essential medicines, access should be increased in-country without quality compromise and this will potentially translate into shortening the time taken for essential medical products to reach patients who need them (16). NMRAs, through the improved regulatory processes, will be better equipped to register products in a streamlined manner (18). In addition, one of the most effective ways of protecting the public from SF medical products in low-income countries is to have practical and pragmatic methods of sharing resources, information and facilities (19). In so doing, NMRAs will be able to make better use of improved technical skills, improved quality of inspections, and have enhanced control over medical products in circulation (18).

There are sound arguments for medical product regulatory harmonisation from both a theoretical and a practical perspective (34). Theoretically, harmonisation enables NMRAs to "level up" to international best practices and standards (34). There is clear science backing pharmaceutical production and product quality assurance, and NMRAs can implement these international standards that exist for various processes and medical products (34). Collaboration allows NMRAs to gain access to information on these international best practices and diminishes the requirement for divergent national procedures (34). Through harmonisation, African NMRAs can leverage international expertise, stay up to date with international trends and standards, and operate efficiently in a resource constrained environment through information sharing and the recognition of decisions made by mature NMRAs (17,30,39). Harmonisation in Africa would also mean more streamlined communication systems between the AU Member States, encouraging the use of a common regulatory language, international best practices and adaptation to globalisation of the pharmaceutical industry (20). By having common regulatory standards for assessments and inspections, NMRAs are better able to communicate and share regulatory information (19). NMRAs can benefit from reliance on sound international standards as a basis or reference for their own decision making. This ensures that regulatory processes are good quality, effective and based on robust scientific evidence and internationally

accepted standards (34). Furthermore, through the development and implementation of regional medicines regulatory harmonisation, there is an expectation of an accompanying increase in the availability of quality-assured, safe and efficacious medical products for priority and neglected diseases, as well as the expansion of donor reach in Africa, which potentially contributes to the attainment of health related developmental goals (16,18).

NMRAs tend to perform overlapping reviews and inspections of clinical or manufacturing sites for similar purposes (38). Harmonisation therefore helps NMRAs to work more efficiently by allowing them to institute reliance mechanisms, including with their neighbours, and lowers costs by reducing duplication of efforts (5,34,38). By freeing up resources and time in this manner, NMRAs can process marketing authorisation applications faster, speed access to NCEs and focus the available resources on those issues that would deliver the greatest public health value (5). Harmonisation also saves resources needed by each regulator (34). The requisite amount of resources, including expertise, required by each NMRA tends to be considerably greater than what is actually available on the ground (34). In addition, the regulatory capacity in Africa will potentially be improved through joint regional medical product assessments and the inspection of manufacturing sites (18). The other benefits NMRAs potentially accrue from harmonisation include increased capacity, more resource efficient authorisation procedures, enhanced quality of marketing authorisation decisions, and more effective medicines control (34). As NMRAs operate within the context of a country with a government, the national governments also benefit from harmonisation (34). Through harmonisation, national governments stand to (i) save money and increase the use of generic medical products; (ii) implement pooled procurement models as they have an enhanced ability to do so; and (iii) improve public health safety (16,34). Based on past experiences, public services have been upgraded as a result of cooperation and harmonisation initiatives (19). Furthermore, harmonised regulations potentially result in health improvements and socioeconomic development (38). Harmonisation also enables the different stakeholders involved in the regulatory process to reach a common understanding on principles that they should collectively adhere to, such as transparency,

predictability, quality, and reliability (34). Harmonisation mechanisms can be established to create a more efficient, effective and transparent process for the marketing authorisation of medical products as well as for following up medical products that are already in circulation (19). These mechanisms for regional regulatory systems and procedures should result in strengthened regulatory capacity at the country level (19). With time, collaboration and harmonisation facilitates mutual understanding and builds trust among the stakeholders involved (34).

Divergent regulatory approaches contribute significantly to the cost, complexity, and time required to make medical products accessible to patients (38). Additionally, manufacturers will have to generate only one data set for all countries and as a result, this may reduce the amount of experimentation being done on both humans and animals (19). Moreover, harmonisation enables the pharmaceutical industry to benefit from the high levels of compliance with regulatory requirements, increased competition resulting from the new markets and local products being more likely to be accepted for export to foreign markets (17,19,30,39). From the viewpoint of the pharmaceutical industry, harmonisation results in a reduction of duplicative processes, greater transparency in regulatory procedures, fewer delays, optimum resource use, increased experience and knowledge sharing, less clinical trials, and improved market access (16,18,19,34). Harmonisation also results in shorter and more predictable registration processes and timelines, within reasonable limits. This enables manufacturers to access large markets faster, creating an incentive for them to engage in increased product registrations across more countries (16,18,34). Efficient and predictable registration timelines help in the promotion of access to new medical products by encouraging more pharmaceutical companies to register medical products/health technologies in African countries (17). Regulatory harmonisation may make unattractive African markets more attractive (7). Last but not least, patients stand to benefit from regulatory harmonisation (77). Due to harmonisation, healthcare professionals may have access to new medical technologies/innovative products and deliver high levels of care in line with the most recent treatment guidelines (17,39). As a result, patients will have faster

access to quality-assured, safe, efficacious and affordable medical products of high public health value that comply with stringent regulatory requirements (16,17,19,34,39). Enhanced coordination and collaboration benefits patients by ensuring that the regulatory process is driven by the best possible science, standards and practice, resulting in safety improvements, innovation and access (38). Patients may also have a reduced risk of consuming SF medical products as well as have a continuous supply of chronic medical products (17,39).

There are a number of collaboration and harmonisation initiatives in Africa that serve as practical examples to advocate for regulatory harmonisation. In the EAC region, Roche applied to market bevacizumab and trastuzumab in 2015 which was a major milestone for the region's initiative (52). These were not new medicines as the USFDA had first approved bevacizumab in 2004 and trastuzumab in 1998, and both these products were on the WHO's essential medicines list. However, the 2 oncology products had never been registered in any EAC Member State (52). Prior to the establishment of the EAC's initiative, a pharmaceutical manufacturer would have had to complete registration applications to each member state. Roche however managed to apply for a single region-wide joint assessment of the medical products making it the first ever to be performed in the region. The products were recommended for registration throughout the EAC region and mainland Tanzania used the positive joint assessment and recommendation to register the medicines within 4 months of application (52). This was a significant improvement over the 24 month average registration time in the region prior to the launch of the initiative (52). Kenya and Uganda were next to register the medicines making it 3 countries that had registered the products. Although the medicines were eligible for registration in all EAC Member States, Roche decided to seek marketing authorisation in only these countries (52). Due to this approach to product assessment, the EAC countries managed to have these medicines available sooner than they typically would and this was beneficial to the patients who now had earlier access to the medicines. Roche also benefited from efficient registrations in multiple countries while it still had patent protection on the medicines, and the EAC NMRAs saved time and resources by performing a single joint assessment instead of having

multiple assessments done at national level (52). In addition, following the implementation of joint dossier assessments in the EAC region, the median timeline from dossier submissions to national marketing authorisation was reduced to 7 months in 2015/16 from a previous 12-24 months (52). Janssen Pharmaceutica Inc. also conducted a study which demonstrated approval time reductions of 40-60% for several branded medicines through joint dossier assessments in the EAC region (9,10).

In the SADC region, the median timeline from dossier submissions to national marketing authorisation was reduced to 8 months by the Zazibona approach (9). Furthermore, the improved product development joint review and GCP inspection timelines have played a pivotal role in ensuring timely regulatory authorisation and approvals of MenAfriVac®, the meningococcal A conjugate vaccine whose dissemination in the meningitis belt of Africa has eliminated epidemic meningitis due to Group A *Neisseria meningitides* as a public health threat (10). A joint review approach has also been used for coordinating and expediting the review of a multi-country Phase III clinical trial for RTS,S/AS01, which is the lead malaria candidate vaccine (10). Furthermore, medicines regulatory harmonisation facilitates ongoing capacity building by having assessors receive peer learning and feedback (7). It is also important for other measures to be adopted, in addition to harmonisation at the regional levels, that will improve the efficiency, effectiveness and timeliness of regulatory activities such as the participation in the WHO-PQP (6). For regulators, participation in the WHO-PQP provides a platform for trust and capacity building (13).

3.4.5 The Challenges of Medicines Regulatory Harmonisation in Africa

In the majority of RECs, there are regional treaties and protocols for medical products regulatory harmonisation (6,18). However, RECs continue to operate individually without cooperation/collaboration (16), and the levels of determination and political commitment demonstrated by countries towards domesticating these regional treaties varies (6,19). As these treaties are not self-executing and require domestication through national laws, the implementation of these agreed upon regional decisions remains a challenge at country level (18).

Therefore, at country level, there is a need to have implementing policies, legislation and regulations that allow the fulfilment of treaty obligations (6). Regulatory frameworks and legislation are created at a national level in countries where they exist and therefore neighbouring countries can have considerably different procedures and systems for regulating as well as approving medical products (6,14,15). Unless harmonisation is effected administratively, countries have no obligation to adopt regulatory decisions that have been made in another country even in cases where the NMRAs receive evidence dossiers that are identical and the region has similar disease patterns (6,15). As a result, researchers and manufacturers experience delays as they must navigate myriad regulatory systems across countries to register the same medical product (6,14,15,35). They must submit duplicative evidence dossiers with several NMRAs for medical product registration in all countries where the product could have a public health impact (6,14,15,35). Each dossier submission costs time, money and delays access to medical products (6,15). In addition, where regulatory harmonisation is not commonplace, these challenges faced by manufacturers lead to a reduction in access to medical products and subsequent price increases due to reduced competition as certain companies opt out of specific markets (8). In order to develop the African pharmaceutical sector, there needs to be market optimisation for new medical products/health technologies (13). The lack of regulatory policy harmonisation between countries also hinders opportunities for NMRA collaboration and reciprocal decision making, resulting in regulatory backlogs and NMRA staff duplicating efforts (6,15).

Regulatory harmonisation in Africa is a challenge as a result of the wide array of regulatory environments and capacities that exist which impede access to essential medicines (8). Countries also have different sovereign approaches to their legal and regulatory frameworks based on their own sociocultural values, historical and political landscapes (38). In addition, regulatory divergence across borders can be a result of differences in the degree of acceptable risks and benefits, burden of diseases, vulnerable populations, privacy concerns, and costs (38). NMRAs also have inadequate resources and therefore, they struggle to retain the requisite quality and number of experts to execute their mandate in the

present day context of rapid advances in the volume and complexity of medical products (38). Harmonisation is made more challenging by gaps in the development of a unified regulatory science body and the availability of a competent regulatory workforce (38). In order for medical products regulation to be effective and yield the envisaged benefits, all aspects of regulation must be addressed (19), and regulators should adapt harmonisation activities based on local circumstances (20). It is also important for harmonisation to balance and take into consideration the different commercial, regulatory and healthcare interests (13).

Regulatory harmonisation in Africa is essentially an SSC initiative. In Africa, SSC initiatives have faced challenges such as poor coordination, inadequate political commitment, unconducive policy environments, language barriers and insufficient financing opportunities (79). Additionally, SSC initiatives face challenges such as a dearth of evidence from SSC implementation in other regions, a paucity of the requisite information for the monitoring and evaluation of outcomes and the impact of SSC initiatives, as well as a regional oversight mechanism for issues such as licensing of health workers and essential medicines regulation. These all need addressing in order to benefit from the numerous opportunities presented by SSC activities (79). Therefore, streamlined use of SSC mechanisms in Africa for health systems strengthening and the delivery of public health services requires the establishment of national and regional institutional mechanisms for coordinating, monitoring and evaluating SSC activities (79). Establishing a framework for effectively implementing the foregoing requires multiple stakeholders to be involved, such as RECs, governments, the private sector and academia (79). These stakeholders can collectively establish SSC mechanisms, provide technical/financial assistance, advocate for their member states and other interests, as well as strengthen policy dialogue and resource mobilisation for health SSC (79). As the main duty bearers of the health development agenda, African countries should provide the overall leadership for public health SSC implementation (79). SSC provides an opportunity for the strengthening of national ownership, self-reliance and harnessing the existing

capacities to address shared African public health challenges. It also assists in the attainment of post-2015 health development agenda goals and SDG targets (79).

The barriers to regional regulatory harmonisation can be classified as barriers in: (i) governance and leadership; (ii) NMRA capacities; (iii) financial resources; (iv) political will; (v) intra-regional relationships; (vi) differences in risk-benefit analysis; and (vii) legal frameworks (20). Lessons can be learned from the challenges faced in the implementation of medicines regulatory harmonisation initiatives of SADC, ECOWAS, EAC, and ASEAN. Drawing lessons from the SADC region, potential barriers to regulatory harmonisation relate to NMRA organisational structures, different legislative and regulatory provisions and different levels of technical capacity (20). In terms of guidance documents and legal frameworks, NMRAs use different ones and this is a challenge for harmonisation (20). There are also differences in legal issues, laws and infrastructure (20). Furthermore, guidelines, which are a foundation for harmonisation, need to be trusted and lack of faith in them leads to resistance in adopting them, and harmonisation therefore cannot proceed in the region (20). Another barrier to regulatory harmonisation is the differences in risk-benefit decisions and interpretation of legislation that NMRAs make for regulatory and product approvals (20). For instance, the AU Model Law on Medical Products Regulation is being interpreted, domesticated and implemented differently according to the local context and needs (20). Even in situations where the same legal and scientific frameworks are used, NMRAs are going to have different priorities in terms of risks and benefits during medical product regulation (20). NMRAs take into consideration their local population and epidemiological needs when making marketing authorisation decisions based on the efficacy and side effect profile of the products in question (20). In addition, the fact that the final decision is still the prerogative of each NMRA is in itself a challenge for harmonisation (20).

The SADC Secretariat, who serve as the region's leadership, have in the past stated that they would support harmonisation activities once the initiative yields positive results (20). At the time, the SADC Secretariat was not convinced that

there was a need to initiate harmonisation as the bureaucracy within the SADC structure would not enable swift turnaround of efforts (20). Instead, the SADC Secretariat envisaged a situation whereby NMRAs initiate harmonisation activities themselves, and at a later stage request the SADC Secretariat to facilitate engagements with the wider regional community (20). This example of a lack of support from leadership presents another challenge in regulatory harmonisation. In the past, some SADC Member States have also decided not to participate in regional harmonisation activities because they had other regulatory activities of higher priority and did not want to side-line their own growth (20). Secondly, these SADC Member States would have saved insignificant amounts of time from the joint medicines registration processes (20). The SADC Member States that had surpassed the minimum standards stipulated for harmonisation preferred to provide guidance to less developed NMRAs as "observers" in harmonisation initiatives because, in their opinions, full participation in harmonisation initiatives would be too time-consuming (20). Member states do agree that cohesion and growth in the region can be improved by cooperation and mutual recognition (20). However, countries such as South Africa which contributes the highest gross domestic product in the region and Zimbabwe are perceived by some as being the region's "political engine". Therefore there is a risk of this perception being a barrier to harmonisation as they can be seen as taking control and imposing their views on SADC Member States (20). There is also a perception that some SADC Member States have low governance and transparency standards, which affects intra-SADC relationships and consequently, harmonisation efforts (20).

The SADC region is culturally diverse and has different languages which potentially acts as a barrier to harmonisation in the region (20). The majority of SADC Member States have English as their official language; however, some member states such as Mozambique and Angola use Portuguese and others, e.g. the Democratic Republic of Congo, use French (20). Cultural and language differences may present communication challenges in harmonisation efforts (20). The reliance on donor funding also poses a challenge for the implementation of harmonisation initiatives as there is a lack of financial sustainability (7). There

are also human resource limitations within the SADC NMRAs which present a challenge to harmonisation (7,20). The experts engaged in regulatory affairs may not have an internationally acceptable level and standard of training (20). Despite all these barriers to regulatory harmonisation in the SADC region, the majority of NMRAs, regardless of size and capacity, are enthusiastic about harmonisation even though progress is slow (20). Prior to undertaking harmonisation, SADC Member States should first prioritise the adoption of minimum standards, information sharing initiatives, and convergence (20). Compared to harmonisation, convergence has a broader view as it focuses on the practicality of harmonisation instead of the standards and formats involved (20). At the time, the more mature NMRAs in the SADC region expressed that convergence should be the focus for the region as a stepping stone towards future harmonisation (20). More recent challenges faced by the SADC's regional harmonisation initiative have already been highlighted in section 2.3.2.2 of this thesis.

According to a study done by Kamwanja et al. (26) in the ECOWAS region, the challenges faced in the harmonisation of the medicines registration agenda are:

i. limited human capital resources, both in terms of numbers and skills, at the Secretariats and in member states;
ii. varied physical facilities in the member states requiring expansion to cater for the full spectrum of regulatory functions;
iii. inadequate quality control laboratories in most NMRAs, with a few being prequalified by WHO;
iv. varying and inadequate Information Communication Systems among member states;
v. insufficient funding particularly for small NMRAs; and
vi. regional discussions are at times not domesticated by member states and as a result, decisions made by individuals are seldom recognised by the other member states (26).

To facilitate better harmonisation of medicine registrations, the region has to address the challenges it grapples with relating to legislative frameworks, medical product registrations, information sharing and capacity building (26).

Like the SADC region, the EAC region has no license that is valid for use in all its member states and the different NMRAs have the sole responsibility of granting marketing authorisations, even for products that have undergone the joint assessment procedure (7,52,80). By law, manufacturers must submit an application and pay a fee to each of the EAC's NMRAs where marketing authorisation is sought (52). Import and export licenses are also required to transport medical products across borders (7). In addition to these challenges, the EAC member states have implemented higher levels of quality control in their harmonisation initiatives (7,52). Their joint assessments require bioequivalence studies, whereas applications for marketing authorisation through national marketing authorisation pathways tend to waive such requirements (7,52). Naturally, applicants are not likely to use the joint procedure presenting an impediment to harmonisation. Although it is commendable that the EAC region is enforcing evidence requirements of quality-assured medical products through its joint procedures, if the local pharmaceutical manufacturers are not receiving assistance with the bioequivalence studies provision, then the regional harmonisation initiative only serves to give multinational companies an advantage while increasing the vulnerability of the small, local pharmaceutical manufacturers (7). By having improved regulation with more advanced requirements, it will potentially curb the marketing of SF medical products; however, there is the possibility of an unintended consequence of an increase in medical product prices (19). In addition, some EAC NMRAs refuse to accept a joint decision indicating that they have not truly embraced the regulatory harmonisation initiative (7). This might be due to the economic model of NMRAs; NMRAs obtain their funds from different sources including from government fees levied by NMRAs, donors and the pharmaceutical industry (20). In relation to the pharmaceutical industry, NMRAs obtain a significant portion of their funds from conducting GMP assessments, dossier reviews and other regulatory functions (7). However, regardless of the source of funds, a recurring theme in regulatory harmonisation is that sustainable financing is a considerable challenge for harmonisation efforts (20). Another challenge is that the cost savings that harmonisation strives to deliver might not improve economic

realities of conducting business in certain markets (7). The pharmaceutical industry has consistently reported that smaller markets such as the EAC region are still unattractive even after harmonisation as they have political instability and logistical problems related to an absence of wholesalers or local distributors (7). Furthermore, some manufacturers and importers are discouraged from swiftly registering their medical products throughout the EAC, particularly in the region's smaller markets, by the lack of a centralised application process and a legally binding mutual recognition framework (52). For the EAC regional harmonisation initiative to be successful, it requires improvements and sustained political commitment (7). Harmonisation is often adopted in theory by countries and harmonisation initiatives tend to fail due to an absence of enforced legislation, participation and resources to perform (20). The desire and ability of a country to engage in regional harmonisation will be influenced by health and pharmaceutical sector policies, the state of professional pharmacy practice, and the state of the local pharmaceutical production sector (34).

In the ASEAN region, there are comprehensive technical guidelines for the regulation of medical products and the ASEAN NMRAs have adopted the ASEAN Common Technical Document (ACTD) (34). However, the ASEAN region lacks strong supervisory support for regulatory harmonisation initiatives resulting in a fragmented approach to harmonisation (34). Where there is insufficient accountability, harmonisation initiatives are not implemented (20). The regulators continue to face challenges which are mainly human resource related: there is a lack of expertise to evaluate dossiers, a lack of experience in evaluating dossiers for innovative medical products, as well as NMRA understaffing (34). The NMRAs opt to have external contract experts which prevents them from building up their own regulatory capacity in the long term (34). In addition, the ASEAN region faces challenges with implementation of harmonisation initiatives, including the ACTD, and some country-specific requirements remain. As seen with other regions, the ASEAN region also has unsustainable funding and resources for harmonisation (34). Over the medium term, and regardless of increased financial resource allocations to regulatory

development within a region, the availability of competent human resources for harmonisation initiatives could remain a challenge (19).

Garnering support for regulatory harmonisation is riddled with challenges (74). There are several competing priorities for political and financial support, particularly as the duty bearers and donors deal with the global financial crisis (74). Although these challenges exist, regional harmonisation is possible and is occurring. In the EAC and SADC regions, NMRAs have jointly assessed dossiers through collaborative regulatory procedures (CRP) (9). The NMRAs in these RECs have also conducted joint GMP inspections to enable faster marketing authorisation (9). In the EAC region, CRP work has resulted in a 40-60% reduction in medicine approval timelines for a number of branded medicines (9). Additionally, the SADC region's Zazibona initiative has demonstrated that work sharing can successfully occur due to leadership commitment, consistency and ownership (81). Through Zazibona: medicine registration has become faster than it would if NMRAs worked independently, maximum output has resulted from sharing limited resources, and NMRAs have benefitted from capacity building (81). Despite the challenges outlined, the value of regulatory systems to global health must continue to be communicated, in addition to coordinating and leveraging the capacity building initiatives that exist (74). Therefore, the AMA can capitalise on these already existing harmonisation initiatives to work in an effective manner towards the accomplishment of its objectives (36). Moreover, the AMA can potentially overcome these harmonisation challenges and facilitate harmonisation by galvanising technical support, regulatory expertise and resources at a scale that neither the national nor regional initiatives can match (3).

3.5 The African Union Model Law on Medical Products Regulation

3.5.1 The Development of the AU Model Law

Health technology regulations are a crucial constituent of every nation's public health system, ensuring access to quality-assured, safe and efficacious health technologies for those who require them most (14,15). However, and as previously alluded to, the capacity to evaluate, approve and monitor the quality,

safety and efficacy of health technologies in many LMICs is limited because of scarce resources, overburdened staff and incoherent policy frameworks (6,14,15). In addition, in countries where it exists, regulatory legislation is created at a national level. Therefore, neighbouring countries in RECs can have considerably different procedures and systems for regulating as well as approving health technologies (6,14,15). Even in cases where the NMRAs receive evidence dossiers that are identical, countries have no obligation to adopt regulatory decisions that have been made in another country (6,15). As a result, researchers and manufacturers experience delays as they must navigate myriad regulatory systems across countries to register the same health technology (6,14,15,35). Each submission of a dossier has time and cost implications, and delays access to health technologies (6,15). Hindering opportunities for NMRA collaboration and reciprocal decision making, the lack of regulatory policy harmonisation between countries leads to regulatory backlogs and NMRA staff duplicating efforts (6,15).

Over the years, the AU has provided support for harmonisation of regulations and some RECs now have streamlined regulatory systems (15). Fully exploiting this momentum, the AUDA-NEPAD and key stakeholders developed the AU Model Law on Medical Products Regulation, hereafter referred to as the AU Model Law, with the aim of ensuring the promotion of innovation and access to new health technologies (14,15). The goal of this non-prescriptive model legislation is to make regulatory systems more efficient and effective as well as facilitate the overall regional harmonisation process (6,9,10,14,15,20,31,53). The development of the draft AU Model Law was done through the AMRH initiative platform and endorsed by the PAP Committee on Health, Labour and Social Affairs (13,53). In November 2015, the AU technical committee on Justice and Legal Affairs approved the AU Model Law which is available for use as a starting point for the establishment of regulatory bodies and providing support for legislation in AU Member States (20,53). A unique attribute of the AU Model Law process is the extensive multi-stakeholder consultations and participation in the legislation development which took place between 2014 and 2015 (13,14). The AU Model Law process is not a standalone development; it complements partnerships, regional integration ventures, the incorporation of global best

practices in medical products regulation, the PMPA as well as the Roadmap for Shared Responsibility for the AIDS, Tuberculosis and Malaria Response in Africa (14). All these elements will potentially ensure the relevance and sustainability of the AU Model Law (14).

The AU Heads of State and Government recognise the importance of regulatory systems that are both efficient and aligned in ensuring access to health technologies, and they adopted the AU Model Law (15). In January 2016, the AU Model Law was officially endorsed at the AU Summit in Addis Ababa, Ethiopia by the AU Heads of State and Government (9,14,21,40,66). In this context of the AU Model Law, health technologies generally refers to medicines, diagnostic tools and vaccines that are suitable for the prevention, treatment or cure of tuberculosis, malaria and Neglected Tropical Diseases (NTDs), but are not yet available for introduction into the market or have not been introduced in low-income countries (14).

The AU Model Law is a tool for the provision of policy and technical guidance to member states and RECs in line with recommendations of the WHO and international standards of quality and safety (6,14,15,31). It is comprehensive legislation meant to be domesticated and implemented by member states and RECs for regulatory systems harmonisation, increasing collaboration across countries, and providing a regulatory environment that is conducive for health technology development and scale up (6,14,15,20,31). Access to quality-assured, safe and efficacious health technologies has been a significant challenge in Africa for decades, partly as a result of weak or absent regulatory systems, and the intention with the AU Model Law is to catalyse access to these lifesaving health technologies in addition to ensuring that health technologies that hold promise are developed, tested, and scaled up for the improvement of health impact (14,15,31) In addition, the AU Model Law was developed and promoted by AUDA-NEPAD to provide the national legislative framework for harmonisation at the regional and sub-regional level, as well as to increase efficiencies in regional, sub-regional and national procedures (6,31). Following the endorsement of the AU Model Law, the next steps have been to engage with RECs, ROs, and

member states to update and enact regional legal frameworks and national laws on the regulation of health technologies (9,14,66). Through the AU Model Law domestication process, a country can adapt the AU Model Law so that it is consistent with its constitutional principles and legal system, as well as amend or repeal any inconsistent national laws (10,15,31,56). The AU Model Law essentially strives to ensure that national laws are in line with international quality and safety standards and that the regulation of health technologies is effective (10,14,15,31). The AU Model Law also supports the AU's desire to promote local pharmaceutical production with the goal of public health protection and economic growth (6). The key components of the AU Model Law are presented in Figure 4.

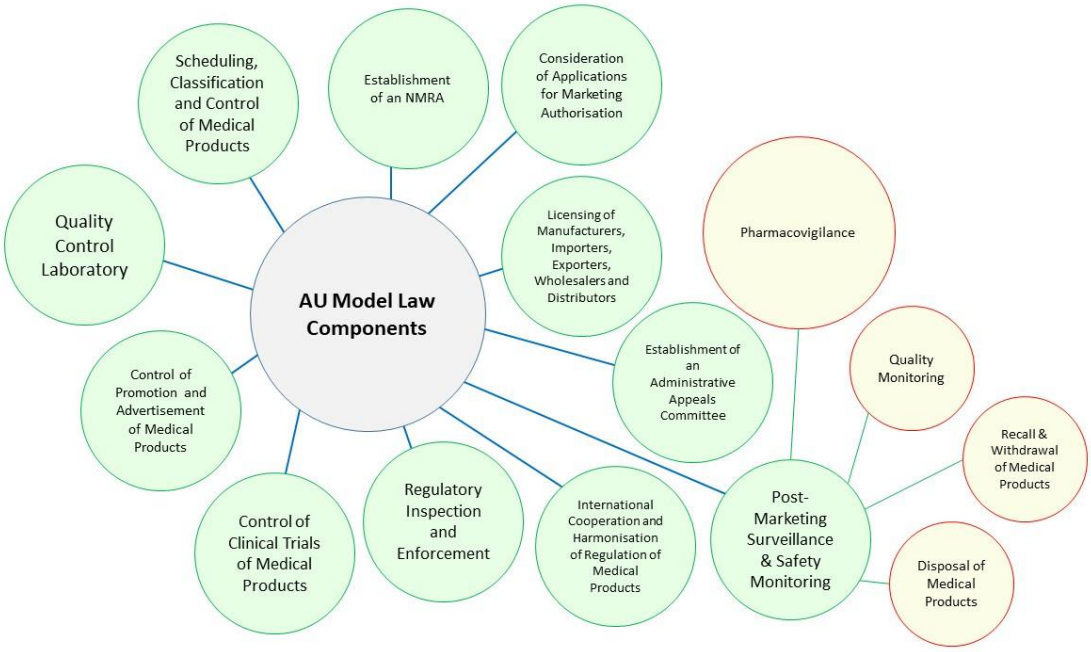

Figure 3: Key Components of the AU Model Law.

3.5.2 Expectations Set by the AU Model Law

According to the AU Model Law, there is an expectation that each AU Member State has an autonomous NMRA that has the authority to regulate medical products/health technologies in terms of product manufacture, import, export, distribution, and use (14,15). In addition, the NMRA is also mandated to authorise clinical trials, grant manufacturing licenses, and set standards for

appropriate new medical product/health technology use (15). Furthermore, the AU Model Law outlines expectations and standards for:

i. marketing health products: every medical product must be registered and have valid marketing authorisation;
ii. licensing: a person or company can only manufacture or distribute medical products/health technologies if they possess a license from the NMRA to do so;
iii. quality and safety of health technologies: NMRAs are mandated to monitor and analyse adverse effects of health technologies in circulation, as well as those being used in clinical trials, and to recall or withdraw any substandard products;
iv. clinical trials: a clinical trial that involves human participants requires clearance from a National Ethics Committee or Institutional Review Board and must be authorised by the NMRA; and
v. Appeal Procedures: an Administrative Appeals Committee needs to be established to hear cases that are filed against the NMRA (14,15,82).

The AU Model Law, by setting expectations for NMRA cooperation at both the national and regional level, requires all NMRAs to participate in regulatory harmonisation initiatives, which includes partaking in reciprocal registrations as well as capacity strengthening efforts (15). NMRAs should also share information with each other on medical products that pose a risk to public health (15). Furthermore, the AU Model Law supports countries to incorporate powers to levy, collect, and use fees for services rendered when reviewing or enacting their laws as well as delivers an enabling regulatory environment for the private sector to provide the African population with medical products (21,25). There is also a need for the legal mandate to be backed by an appropriate, transparent and process-oriented fee structure development which is commensurate with the required regulatory workload (25).

3.5.3 Country Level Adoption and Implementation of the AU Model Law

In Dakar, Senegal, AUDA-NEPAD, being the technical arm of the AU with the mandate of spearheading policy implementation frameworks and policy harmonization, convened a TWG on Medicines Policy and Regulatory Reforms (MPRR) (6,10,14,37,66). The TWG, which met in April and September 2013, was composed of legal experts, regulators, strategic stakeholders, partners from RECs/ROs, and obtained technical assistance from UNDP, UNAIDS, WHO as well as other partners (6,10,14,40,66). The aim was to brainstorm and develop key activities to aid AU Model Law implementation, to deliberate on the modalities for targeted interventions at the national level, and to optimise access to, and the delivery of, new health technologies that are quality-assured, safe and efficacious (14,66). Advocated for by the AMRH initiative, this approach acknowledges the indisputable importance of RECs and ROs being engaged in the advancement of regulatory harmonisation efforts in their respective regions (66). In addition, this approach aims for enhanced policy coherence in RECs and AU Member States for public health and pharmaceutical sector advancement by focusing on the alignment of policies and regulatory reforms (66). The TWG on MPRR has resulted in the development of regional roadmaps and action plans that seek to guide AU Model Law implementation at the national as well as regional level (10,66). In an attempt to use the AU Model Law in an optimum manner to attain harmonisation with other member states, RECs and ROs are conducting preliminary needs assessments of their respective countries and subsequently developing S.W.O.T reports to respond to regulatory needs (66).

The implementation targets for the AU Model Law at the national and regional level were to have at least three regions adopting regional policies and legal frameworks for medical product regulation by 2020 (66), and at least 25 countries domesticating the AU Model Law by 2020 (10,14,66). It was suggested that AU Member States: (i) commission and provide support for thorough needs assessments of their respective national regulatory contexts as part of preparing for the AU Model Law domestication; (ii) review regional roadmaps and action plans with an aim of developing harmonised national roadmaps and action plans

for AU Model Law domestication; and (iii) enact the AU Model Law, a version of it or parts of it, that contribute to national regulatory systems strengthening and drives Africa's harmonisation agenda (10,66). For the successful implementation of the AU Model Law, RECs, ROs and Member States were encouraged to carry out a combination of preliminary situational and needs assessments on the existent regulatory systems, which includes existing frameworks, in individual countries using the AU Model Law as the benchmark (14,66). Based on the gaps that are identified, a roadmap should be developed for AU Model Law implementation that clearly outlines the action plan to address the gaps, and if feasible, RECs should harmonise regulatory requirements for their member states (14,66). The roadmaps and action plans make up a detailed and systematic approach that responds to the preliminary needs assessment results in the individual countries and begin in accordance with the legislative procedures of the specific country (66). There is also a paucity of information on how many countries have laws deemed to be sufficient/comprehensive and already satisfy the AU Model Law requirements. Therefore, research needs to be carried out to address the foregoing as well as to assess countries pre- and post-AU Model Law domestication and implementation.

The implementation of the AU Model Law is anticipated to have an impact on the national regulatory system and the benefits of the implementation can be seen at the technical level as well as at the more general health systems level (66). Regarding the broader health system, the benefits of the implementation of the model law include:

i. having national laws that are up to international standards and best practice, allowing the respective governments to execute their mandate of ensuring that citizens have access to medical products/health technologies as part of their human right to health (15,66);
ii. supporting access to health by ensuring that the requisite medical products are available;
iii. supporting, in the respective country, effective market control for medical products that are in circulation; and

iv. having legal provisions at national level that allow harmonisation regionally with other countries in RECs and international collaboration (66).

By implementing the AU Model Law, AU Member States potentially strengthen national and regional regulatory systems as well as reduce the prevalence of SF medical products through the enforcement of a provision for SF medical product prohibition (10).

The AU Model Law and AMRH efforts are intended to support countries rectify the regulatory challenges that they have been grappling with for many years (15). In countries that have inadequate legislation and regulatory frameworks, the AU Model Law adoption process must be expedited to allow for the establishment of NMRAs that function properly (53). By addressing gaps and inconsistencies in regulatory legislation, while giving priority to harmonisation efforts, AU Member States can catalyse access to innovative and lifesaving medical products (15). The long term goal of the AMRH initiative is to establish the African Medicines Agency, which will have the mandate of overseeing the registration of specific medical products and coordinating regional harmonisation systems in Africa (14,23). Therefore, the development of the AU Model Law should be interpreted within the context of these overarching efforts towards regulatory harmonisation in Africa (14).

3.6 The African Medicines Agency

3.6.1 Establishing the African Medicines Agency

In 2010, the Sixtieth Session of the World Health Organization (WHO) Regional Committee for Africa emphasised the need for strengthening NMRA capacities in order to prevent the circulation and subsequent use of SF medical products. Therefore, it recommended establishing the African Medicines Agency (AMA) in response to the numerous health challenges faced on the continent such as a lack of access to medical products (3,36,48). In addition, in October 2013 the 8th African Vaccine Regulatory Forum (AVAREF) was held in Uganda and in December 2013, the 3rd African Medicines Regulatory Conference (AMRC) was

held in South Africa, with both of them discussing and supporting the establishment of AMA (36,48). In July 2012, the report of AIDS Watch Africa (AWA) Action Committee of Heads of State and Government led to an AU Assembly Declaration, Assembly/AU/Decl.2 (XIX) in which the Council decided that the AMRH initiative shall serve as the foundation for the establishment of AMA (1,3,10,49,58). The successes of the AMRH initiative and AVAREF have provided a conducive environment for R&D, innovation, competition, local pharmaceutical production and market expansion (10). Sustaining the AMRH initiative and/or AVAREF momentum, and having a seamless transition to the AMA, may contribute to the reduction of technical trade barriers particularly at a time when RECs are swiftly moving in the direction of stronger economic integration (10). Improvements in access to medical products can occur following the use of continental institutional, scientific and regulatory resources (33,49).

In Luanda, Angola, key milestones for the establishment of the AMA were endorsed at the First African Ministers of Health Meeting which was jointly convened by the African Union Commission (AUC) and WHO from 14-17 April 2014 (1,10,36,40,47,49). This was in response to the declarations of the African Heads of State and Government {Assembly/AU/Decl.2 (XIX)}, and decisions of the WHO Regional Committee for Africa (47). Decisions made by the AU Summit of Heads of State and Government, host institution/country designation, governing body approval, staff appointments, resource allocation, and the launch of the AMA are some of the milestones included (AUC/WHO/2014/Doc.2) (36,47). The African Ministers of Health committed to: (i) prioritising investments for the development of regulatory capacity; (ii) pursuing convergence and harmonisation of medical products regulation in RECs; and (iii) resource allocation for AMA operationalisation (1,10,40,47,49). In addition, AUC and WHO were requested by the Ministers of Health to establish a Task Team, in collaboration with relevant stakeholders, that would facilitate implementation of the milestones with consideration being given to regional representation and required skills (36,47). The establishment of the Task Team

was endorsed in January 2015 by the Executive Council. The Council also mandated the AUC, NEPAD and WHO to serve as a Joint Secretariat (40).

In Africa, regulatory systems in some countries are better than in others (14,36,48). These regulatory capacity disparities further support and justify the establishment of the African Medicines Agency (36,48). To effectively address some of the challenges that are being faced by African countries, AU Member States are establishing the AMA to overcome these challenges which include:

i. implementing agreed procedures and processes,
ii. coordinating regulatory practices across sub-regions,
iii. priority setting for medical products against select diseases,
iv. pharmaceutical manufacturing promotion and,
v. optimally using the limited resources available to NMRAs (3,36,48).

The AU Executive Council Decision EX.CL/Dec.857 (XXVI) of January 2015 forms the basis for the establishment of AMA and endorsed the milestones for establishing the Agency within the context of the AMRH initiative, which is a part of the PMPA's implementation (10,40,50). In Africa, there are also several donors (The Global Fund to Fight AIDS, TB and Malaria; Global Alliance for Vaccines and Immunization; UN Commission for Life-saving Commodities for Maternal, Reproductive and Child Health; and the Neglected Tropical Diseases Partnership) and networks for regulators (AVAREF and AMRC) which aim to enhance the availability of medical products and serve as opportunities for enhancing regulatory convergence at a continental level, therefore requiring AMA to be established for regulatory oversight (3,36,48). In addition, after recognising the necessity of a harmonised mechanism for medical products regulation, African countries are establishing AMA to fulfil that need (36,48). Moreover, the alignment of regulatory systems strengthening efforts, harmonisation initiatives and advocating for AMA's establishment are important for optimising pharmaceutical markets as well as ensuring the sustainable supply of medical products for priority and neglected diseases (10).The historical context of the African Medicines Agency is shown in Figure 5.

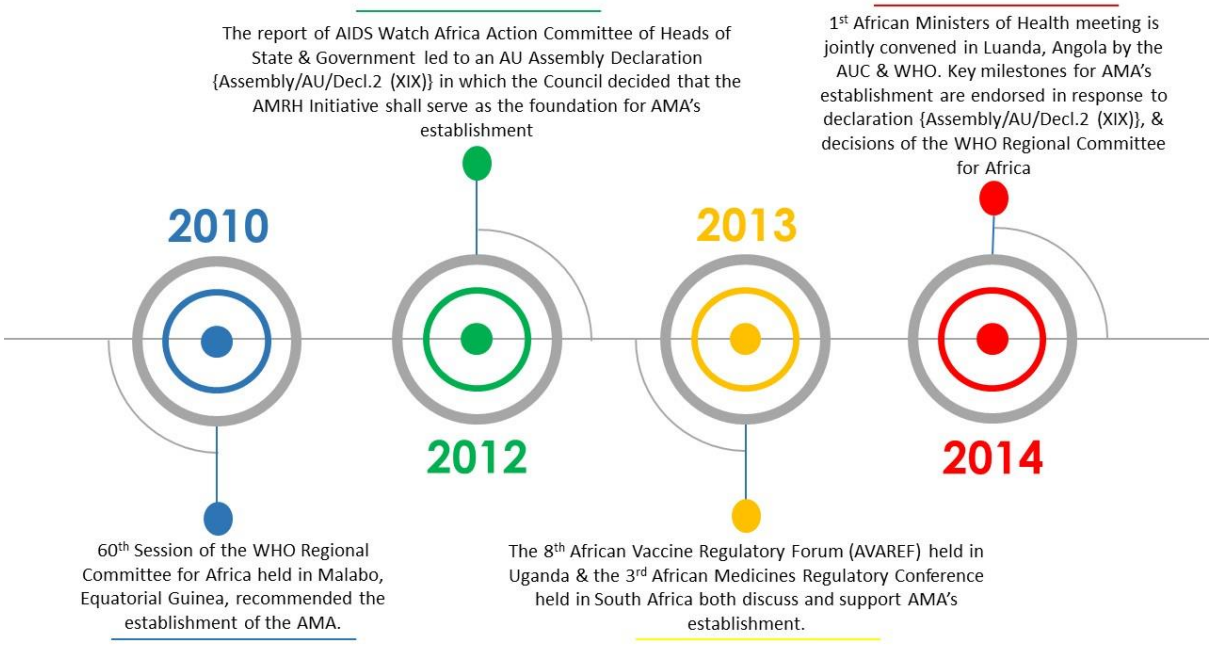

Figure 4: The Historical Context of the African Medicines Agency.

3.6.2 The African Medicines Agency Treaty

In parallel and to support the AMRH initiative, the AU, WHO and NEPAD were collaborating to ensure that the AU Heads of State and Government endorse the establishment of AMA in 2018 (37). AMA was expected to be launched in 2018 (31,36), with efforts being made to ensure that the Agency capitalises on already existent mechanisms, experiences and technology to work in an effective manner towards the accomplishment of its objectives (36). The establishment of AMA builds upon pre-existing structures of RECs and AU Member States that are already implementing AMRH initiative programs within the PMPA framework (31). AMA is to be established by a treaty which has taken into consideration key AU decisions, declarations and policy frameworks including the 55th Decision of the African Union {Assembly/AU/Dec.55 (IV)} taken during the Abuja Summit 2005 and the 19th Ordinary Session Decision of the Assembly {Assembly AU/Dec.442(XIX)}, Pillar II which requested the AU Roadmap on Shared Responsibility and Global Solidarity for AIDS, TB and Malaria Response in Africa (1,6,40). On 11 February 2019, the AU Assembly, during their 32nd Ordinary Session in Addis Ababa, Ethiopia, adopted the African Medicines Agency treaty (11,50,59,60). The treaty for the establishment of AMA was then

unanimously adopted by the African Ministers of Health gathered at the 71st World Health Assembly in Geneva (33,58).

In the context of moving towards the establishment of the AMA, the treaty must be signed and then ratified. Ratification refers to the national procedure where the AU Member State puts in place a law that allows for the implementation of the AMA treaty (64). The AMA treaty is open to AU Member States for signature and ratification/accession and it shall enter into force thirty days after the deposition of the fifteenth instrument of ratification/accession (11,49,50,59–62). The instrument of ratification/accession to the present treaty, which is available in Arabic, English, French and Portuguese (62), shall be deposited with the Chairperson of the Commission, who then has the role of notifying all AU Member States of the deposition of the ratification/accession instrument (49,59,62). Invitations shall be sent to members of the Conference of the Party to the Treaty to place a bid to host the Agency (1,50,61). In order to host AMA, the AU Member State must ensure the provision of conditions that are supportive of AMA's regulatory and coordinating role and be optimal for the Agency to execute its mandate (3). After an assessment of all the bids to host the Agency, a report shall be presented to the Assembly of the Heads of State and Government for a decision on the hosting of the Agency; thereafter AMA shall begin operations (1,50,61). Demonstrating their determination to rectify the regulatory challenges faced in Africa, African health leaders are adopting the treaty and on 12 June 2019, the Republic of Rwanda became the first AU Member State to sign the treaty (1,58,59). For AU Member States who accede to the present treaty, the AMA treaty shall be in force, in respect to that member state, on the date of deposition of the accession instrument (49). Africa needs robust institutions that can address challenges related to access to quality-assured, safe and efficacious medical products and health technologies. The establishment of AMA is therefore considered to be an important step towards that objective (10). The proposed structure of the AMA is illustrated in Figure 6.

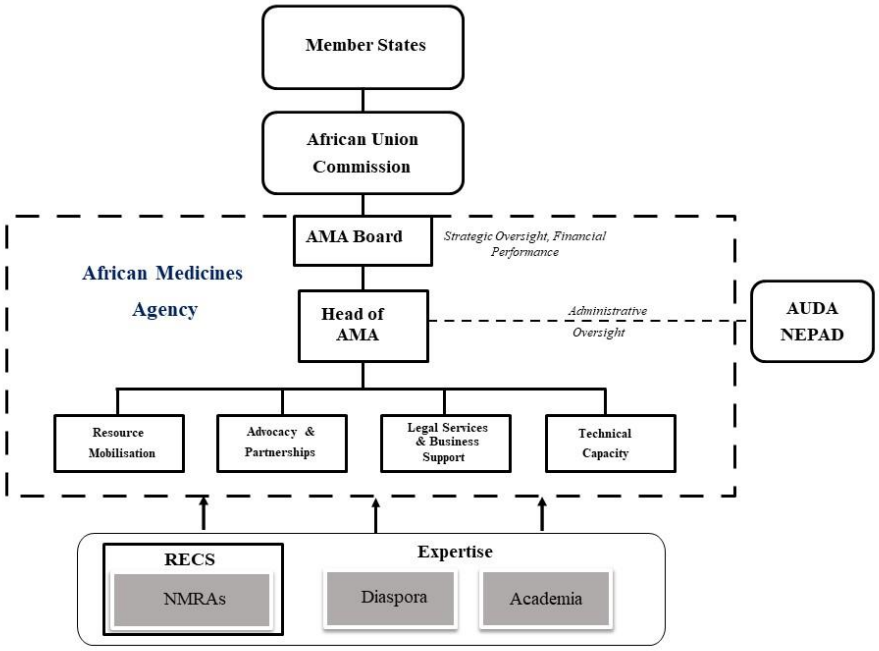

Figure 5: The Proposed Structure of the African Medicines Agency.

For any regional or continental body to be successful, there needs to be political will from the countries involved to relinquish some sovereignty for the prioritisation of regional or continental interests over national interests (3). The implementation of regional or continental decisions is oftentimes impeded by varying commitment levels to the regional or continental initiatives and at lower levels of integration, misconceptions should be resolved along with any differences in policy (3,8). Several factors exist that are influential when considering the establishment and subsequent success of AMA and these include:

i. language barriers: the AU has at least six official languages with some RECs having more than two official languages;
ii. the creation of an African Continental Free Trade Area (AfCFTA): progress in this regard will have an impact on AMA's progress as the agency's activities will be conducted within the context of regional/continental integration;
iii. the functionality of Regional Centres of Regulatory Excellence (RCOREs): regulatory capacity at NMRAs can be built through the optimum use of the established RCOREs;

iv. political and policy leadership to support efforts in harmonisation at the AU and RECs; and
v. sustainable financing mechanisms (3).

In order to achieve the predetermined targets, key milestones will include an increase in the number of GMP compliant manufacturing facilities, AU Member States and RECs with appropriate policies, legal and regulatory frameworks, NMRAs and RECs with sustainable financing, and an increased market share of local manufacturers in terms of both volume and value (3). The desired results for AMA are considered to be attainable through strategies such as regional integration and harmonisation; national and regional level policy, legal and regulatory reforms which include promoting and advocating for model law use in AU Member States; development of regulatory capacity – human, infrastructure, financial, technical, governance systems; and advocacy and knowledge management (3,33).

3.6.3 The Value Proposition of the African Medicines Agency

Intended to be an organ of the AU that is legally mandated by member states, AMA aims to provide a platform for the coordination and strengthening of ongoing medicines regulatory harmonisation initiatives across the continent (1,3,33,36,40,47,48). AMA, a specialised agency of the AU, plans to ensure the optimal use of scarce resources by pooling expertise, capacities and strengthening existent networks. It is also intended to offer guidance, in addition to complementing and enhancing the harmonisation efforts of RECs. This will theoretically contribute to enhanced accessibility of quality, safe, efficacious and affordable medical products (1,3,33,36,40,47–49,60,61). AU Member States have recommended that the establishment of AMA be done in a stepwise approach that involves the RECs and AUC (36,48). Under the leadership of AMA, efforts in regulatory systems strengthening and harmonisation initiatives can be better coordinated resulting in improved sovereign control, and medicines regulation that allows AU Member States to provide protection for public health more efficiently and effectively particularly against risks associated with SF medical product and health technology use (3,49,59,60). AMA also proposes to

enable expedited approvals for medical products that meet the health needs of Africans, particularly for conditions that affect Africa disproportionately, while also fostering the competitiveness of locally manufactured medical products (3,49). Furthermore, the States Parties and RECs seek to enhance capacity in medical products regulation in order to improve access to medical products for Africans (1,49,60).

3.6.3.1 Vision and Mission of the AMA

The AMA's vision is to ensure that all Africans have access to affordable medical products, that meet internationally recognised quality, safety and efficacy standards, for priority diseases/conditions (3,36,48,59,60). At the continental level, AMA's mission is:

i. to coordinate national and sub-regional medicines regulatory systems;
ii. to conduct regulatory oversight of selected medical products including traditional medicines; and
iii. to promote international cooperation, harmonisation and the mutual recognition of regulatory decisions (3,9,33,36,40,48,59–62).

AMA proposes to work collaboratively with NMRAs, provide technical guidance, reduce duplicative efforts, and ensure cost-effective use of limited resources (9,40,62). In order to achieve its mandate, the AMA also intends to work with technical partners such as WHO, the EMA and U.S. Food and Drug Administration for relevance and participation on normative standards, technical cooperation and capacity building (3). In addition, improved access to quality medical products may result from an enhanced regulatory environment created by AMA (36). The AMA, serving as a reference centre that has a coordination and stewardship function for the regulatory activities of AU Member States, intends to perform the following as part of its core activities: (i) marketing authorisation; (ii) joint assessments and GMP Inspections; (iii) market surveillance; (iv) safety monitoring; (v) oversight of clinical trials; and (vi) coordination of quality control laboratory services (3,36,48,49). As it is governed in accordance with AU rules and procedures, the guiding principles of AMA will be leadership; good governance and stewardship; credibility; value addition;

competency; ownership; transparency and accountability in decision-making; confidentiality; commitment to sound quality management; partnerships and collaboration; and support for innovation (33,36,48,49,62).

3.6.3.2 Medicines Assessment

There is a dearth of information on the extent of the quality and safety of medical products in African countries as a result of inadequate regulatory and post marketing surveillance systems (3). Compared to medicines, the situation for medical devices and *in vitro* diagnostics is postulated to be worse because of the relatively limited capacity to regulate these products (3). Therefore, for functions such as GMP inspections of foreign manufacturers, reviewing complex medical products and multi-country clinical trials, regional agencies and AMA can optimise the resources that are available within the respective regions and harmonise technical requirements, joint activities, work sharing activities, as well as coordinate technical support for AU Member States (3,40,50,60,62). It is worth noting that AMA will not replace NMRAs or the sub-regional medicines regulatory authorities which will be established by RECs (3,10,50,60). Instead, AMA seeks to complement the efforts of NMRAs, RECs and ROs in the process of creating a conducive environment for the pharmaceutical industry to develop through enhanced coordination of the various stakeholders involved in African regulatory harmonisation initiatives (10). NMRAs will still assess the majority of medical products, have their decision making roles and put in place market controls for their specific territories (3,10). As the AU does not have sweeping legal powers over the national jurisdictions of member states, decisions made at the continental level are not legally enforceable in AU Member States (3). In addition, AMA aims to offer regulatory guidance on particular issues that are problematic for which technical capacity and expertise are limited at the national or regional level, e.g. medical device regulation, pharmaceutical e-commerce, and regulation of high technology products (vaccines, biologics, and innovative therapies for pandemics) (3,33,40,60–62). Furthermore, it is important for Africa to establish solid ground for the growth of the pharmaceutical market while leveraging the increased political stability, rapid economic development, increasing public health investments, maturing regulatory environment, and

escalating consumerism (10). Table 3 shows the level of implementation of regulatory functions at the NMRA, regional and AMA level.

Table 3: Level of implementation of regulatory functions at national, regional and continental level (3).

Regulatory function	**NMRA**	**Regional harmonisation**	**AMA**
Registration of Medical Products	X	X[a]	NA
GMP Inspection of Manufacturers	X	X[b]	X[c]
Inspection of Supply Chain (Importers, Wholesalers, Retailers)	X	-	-
Post marketing surveillance	X	X[d]	X[d]
Pharmacovigilance	X	-	-
Regulation of Clinical Trials	X	X[e]	X[f]
Quality Control	X	-	-
Medicine Information	X	-	-

[a] In some RECs, centralised registration may not be feasible as it is dependent on specific regional contexts. In addition, centralised registration will only be for selected products for which centralised registrations would offer a comparative advantage.
[b] The majority of NMRAs do not have the resource capacity to perform GMP inspections. Therefore, this function can ideally be done at both the national and regional level, though NMRAs have the final approval.
[c] In African countries, GMP inspections of API manufacturers, biologics and vaccines is virtually non-existent. Therefore, this function can ideally be coordinated and conducted at the continental level, though NMRAs have the final approval.
[d] Regional agencies and the AMA have the role of coordinating and facilitating information exchange at national, regional and continental level, particularly for SF medical products.
[e] Review and/or coordination of regulatory oversight of multi-country clinical trials.
[f] Regulatory guidance and/or coordination of regulatory oversight of clinical trials for investigative and innovative therapies (e.g. for pandemics such as Ebola and COVID-19).

3.6.4 Developing Regulatory Science Specialists

Regulatory science is "the science that informs, facilitates and/or evaluates regulatory decision-making" (83). It is science applied to medicinal products and focuses on the evaluation of the performance of medicine regulations and

regulatory instruments, the development of tools and methods to back regulatory decision-making, and the generation of evidence that informs regulatory decisions (83). The agenda for the regulation of medical products and harmonisation in Africa is predominantly motivated by the need to increase access to essential medical products and bolster innovation on the continent (63). In order for this need to be realised, a competent healthcare workforce and expertise in regulatory science is required to evaluate the quality, safety, efficacy and performance of medical products (63). However, human and institutional capacity, regulatory standards as well as practices continue to fall short in Africa (63). Additionally, an inadequate and sometimes lacking healthcare workforce, incoherent *ad hoc* regulatory workforce trainings, weak infrastructure, and unsustainable healthcare financing mechanisms have aggravated the situation (63). As a result, a significant number of countries in Africa continue to face challenges related to the delivery of quality healthcare (63). In response, the AMRH initiative has provided support to NMRAs that are on a quest to develop their capacities and regulatory systems to ensure that medical products are quality-assured, safe and efficacious (13). The AMRH initiative also recognises the importance of developing regulatory capacity in order for quality healthcare services to be delivered, and addressing the regulatory capacity challenges that the NMRAs and pharmaceutical industry in Africa experience (10).

The AMRH initiative, through the Continental TWG on Regulatory Capacity Development, developed the criteria for establishing Regional Centres of Regulatory Excellence (RCORE) as part of the mandate of the initiative to develop and strengthen regulatory capacity in Africa (10,13). An RCORE is an institution, or partnership of institutions, with specific expertise in regulatory science, proven capacity as well as capabilities in the training or delivery of services in at least one of the identified categories of regulatory and managerial functions (10,63). These institutions include, but are not limited to, NMRAs, academic institutions, scientific and research institutions, information dissemination centres, and pharmacovigilance centres (63). Since October 2013, calls for expression of interest to become an RCORE have been disseminated and a pool of regulatory experts was launched (13). In 2014, the AMRH initiative,

through NEPAD Agency, started spearheading the designation of 11 RCOREs that specialise in 8 regulatory functions, strengthening the development of regulatory capacity by leveraging existing academic, research and regulatory institutions (9,10,21,31,63).

Currently, the RCOREs that exist are for:

i. Pharmacovigilance: University of Ghana Medical School-WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance; Pharmacy and Poisons Board (PPB), Kenya;
ii. Training in Core Regulatory Functions: St. Luke's Foundation, Tanzania – Kilimanjaro School of Pharmacy; University of Ibadan, Nigeria – Centre for Drug Discovery, Development and Production;
iii. Quality Assurance and Quality Control of Medicines: North West University (NWU) – Potchefstroom Campus, South Africa-WHO Collaborating Centre for the Quality Assurance of Medicines; National Agency for Food and Drug Administration and Control (NAFDAC), Nigeria;
iv. Medicines Registration and Evaluation, Quality Assurance/Quality Control and Clinical Trials Oversight: Medicines Control Authority of Zimbabwe (MCAZ);
v. Licensing of the Manufacture, Import, Export, Distribution and, Inspection and Surveillance of Manufacturers, Importers, Wholesalers and Dispensers of Medicine: National Drug Authority (NDA), Uganda;
vi. Clinical Trials Oversight: University of Ouagadougou, Burkina Faso – Direction General de la Pharmacie du Medicament et les Laboratoires;
vii. Registration and Evaluation and Clinical Trials Oversight: Foods and Drugs Authority (FDA), Ghana; and
viii. Medicine Evaluation and Registration: School of Pharmacy, Muhimbili University of Health and Allied Sciences (MUHAS) – Tanzania Drugs and Food Authority (TFDA) (10,31,63).

Albeit a specialised field, regulatory science grapples with inadequate human resources with unsustainable availabilities, especially in LMICs, which has been

attributed to a lack of financial resources in NMRAs to effectively attract and retain competent staff (3,9,14,15). In addition, there are inflexible recruitment processes, an absence of career structure, lack of incentives, and a brain drain (9). There are also limited opportunities for training in regulatory science, as seen with the very limited academic institutions that provide postgraduate regulatory science programmes (3,9). Therefore, the aim of designated RCOREs is to support a regulatory workforce that enhances human and institutional capacity in the following regulatory functions: pharmacovigilance, training in core regulatory functions, quality assurance, quality control, medicine evaluation and registration, clinical trial oversight, and the licensing, inspection and surveillance of manufacturers, importers and inspections (9,10,31,63). RCOREs focus on developing regulatory science expertise in Africa, which is important to ensure effective regulation of products on the continent. These centres are trendsetters, occupying a pivotal role in the development of competent experts in the emerging fields of medicines regulation (63). Furthermore, RCOREs were developed to make *ad hoc* regulatory training programs more efficient and effective as well as to support AU Member States improve their healthcare delivery, regulatory standards and practices (31,63).

Through partnerships between NMRAs and academic/research institutions, RCOREs have an overarching goal of increasing the regulatory workforce in Africa by using several approaches that focus on the following critical interventions:

i. providing academic and technical training in regulatory science relevant to different regulatory functions and managerial aspects;
ii. enhancing skills through hands-on training, twinning, exchanges and job placements in the pharmaceutical industry as part of practical training (9,10,21,31,63);
iii. spearheading operational research, pilot-testing innovations and interventions to inform best practice; and
iv. promoting and scaling up the above activities (10,31,63).

In terms of the development of the regulatory capacity in Africa, RCOREs have a key role to play as they contribute to the enhancement of the potential of AU Member States to attain a qualified, competent and experienced pharmaceutical sector workforce (63). This will in turn improve the assessment of the quality, safety, efficacy and performance of medical products as well as improve quality assurance and control (63). Having regulatory training programmes for African regulators increases the number of regulatory experts on the continent (18). By producing an adequate and trained healthcare workforce to perform these functions, there will potentially be increased access to essential products in Africa and a reduction of the prevalence of SF medical products (63). Furthermore, RCOREs, through enhancing technical and professional competencies in health, contribute to the Science, Technology and Innovation Strategy for Africa (STISA) 2024, which is a key AU pillar in science, technology, innovation and the development of human capacity (63). In 2019, representatives from the AUDA-NEPAD, RCOREs, United States Agency for International Development (USAID), Medicines, Technologies and Pharmaceutical Services (MTaPS), United States Pharmacopoeia, and FHI360 met in Accra, Ghana to review and validate a monitoring and evaluation tool to measure the performance of the 11 RCOREs (84). However, the findings of these assessments are not yet publicly available. It would be of interest to review these findings and obtain an appreciation of the performance and opportunities and threats of the RCOREs. There are also no independent evaluations of the RCOREs' performance which is a possible weakness of the whole structure.

Extensive theoretical and practical capacity building for NMRA staff is required for effective medicines regulation (40). Therefore, the AMA intends to build on the experiences and strengths of the RCORE model in order to develop regulatory science specialists in Africa (3,33,40,62). There is also a desire for the AMA to create more RCOREs, and support them with curriculum development and training programmes so as to have more specialised and certified regulatory officers for AU Member States and RECs (40). AMA will also promote the adoption and harmonisation of regulatory policies, standards, and scientific guidelines, as well as coordinate existing efforts in regulatory harmonisation in

RECs and ROs (33,40,61,62). Moreover, it will provide regulatory guidance, scientific opinions and a common framework for regulatory actions on medical products, as well as priority and emerging issues and pandemics (33,40,60–62). Providing regulatory recommendations that AU Member States can rely on to make their own decisions, AMA builds on the strengthened capacity of medicines regulation in Africa (1,50). In the event of public health emergencies in Africa, AMA will lead the mobilisation of regulatory expertise for the provision of scientific opinions in consultation with the affected AU Member States where new medical products are to be deployed for investigation purposes and for clinical trials (33,40,62). Most low-income countries, including those in Africa, have not fully exploited the Trade Related Aspects of Intellectual Property Rights (TRIPS) flexibilities and this has been attributed to the technocrats who are tasked with dealing with Intellectual Property Rights (IPR) and access to medicines having a general lack of knowledge on the subject area; secondly, there are capacity constraints that include weak legal and regulatory frameworks, and weak administrative capacity (8). Therefore, having harmonised registrations can assist the AU, through AMA, to effectively use TRIPS flexibilities for the production and import of generic medical products that are protected by patents in one or more African countries (61). The role of NMRAs in IP enforcement is controversial. Accordingly, it is unclear what role the AMA will have in enabling the maximal use of TRIPS flexibilities. Instead of having 54 different NMRAs on the African continent, each with its own regulatory requirements, AMA can deliver value for money, reduce exorbitant medicine costs, and result in streamlined regulatory processes so as to enable the timely evaluation and subsequent registration of medical products (3). As Africa lacks sufficient regulatory capacity, AMA occupies a unique position to harness the resources that are available on the continent to improve access to essential medical products and health technologies, including for those who live in Africa's most remote areas (3,33,58,60). It can also facilitate collaboration in order to reduce duplication of work/effort, regulatory capacity optimisation, and facilitate information exchange (3,40,61,62). Furthermore, AMA represents a single,

credible African voice that has more weight compared to having individual voices on regulatory issues on the continent (3).

3.6.5 Financing the African Medicines Agency

The AMA is expected to devise innovative resource mobilisation methods (62). AU Member States, in addition to serving as the primary source of funds for the AMA, will provide contributions in kind by dedicating part of the time of their NMRA staff to AMA work (3,36,48,50). This is to ensure that AMA has a small critical mass of staff that are competent to enable the work of the experts, and that of their respective committees (3,36). By creating groups of experts that work together transparently, trust may be built between the assessors from different African countries and it ensures that scientific standards are applied consistently system wide. This has been observed in the case of the Working Parties of the EU's Committee for Medicinal Products for Human Use (CHMP) which brings together experts in specific scientific fields which include quality, biologics/biosimilars, and oncology (72). Estimates suggest that in the first five years, a total of US$100 million will be required to fund AMA and this amount will cover staff costs (US$10 million), equipment/infrastructure (US$65 million), and operational costs (US$25 million) (48). In LMICs, some of the finance related challenges that NMRAs face include charging arbitrary amounts as fees that fail to cover value added services, which then impedes market entry, post marketing quality surveillance, reliance efforts, and possible financial sustainability (3,25). The available resources are hardly ever commensurate with the NMRA's needs or expectations and in such scenarios, adopting a risk-based approach is fundamental for the resource allocation (25). A risk-based approach means diverting the available resources to those regulatory functions or activities that have a greater probability of resulting in access to quality-assured medicines, identifying and addressing high-risk quality problems, and achieving maximum impact on the regulatory investments (25). Moreover, the global economic recession in conjunction with the evolving donor priorities have resulted in diminished financial resources available from traditional donors, which all presents a threat to the sustainability of AMA (3,8). Therefore, it is important to

have an implementation plan that is independent of donations when ensuring access to medical products (8).

For there to be effective and long term Agency functioning, it is essential to have clearly defined goals and sustainability institutionalised, especially in terms of both financial and human resources (25). Ensuring that the requisite procedures and resources exist, sustainability will enable AMA to fulfil its mandate in a responsive, outcome oriented, science based, accountable, value-added, and independent manner (25). Financial institutions and development partners may also provide grants, donations and funding to AMA in accordance with guidelines set by the AMA Governing Board. However, such external funding must not put AMA in a situation that may negatively affect its decision making, and AMA should be able to continue to operate as an independent regulatory authority (3,36,48,62). For sustainability to work, any investments obtained externally should concentrate on supporting infrastructure development, strategies, staff and systems as opposed to directly financing operational activities (25). To appropriately finance operations, particularly through revenue generation and retention, NMRAs must have the legal mandate, requisite structures and political will to do so (25). Generating and retaining revenue translates into NMRAs requiring less direct funding from the government and it strengthens accountability as well as functional efficiency (3,25).

3.7 Theoretical Frameworks

The aims of this study are to analyse in-depth the rationale, perceived benefits, enabling factors and challenges of domesticating and implementing the AU Model Law on Medical Products Regulation by AU Member States and of the establishment of the African Medicines Agency. Therefore, two theoretical frameworks were selected to inform data analysis and accomplish this aim. Theoretical frameworks serve the purpose of limiting the scope of the relevant data by focusing on certain variables and defining the specific viewpoint of the researcher in data analysis and interpretation (85). Additionally, theoretical frameworks enable the understanding of concepts and variables according to set definitions and facilitate the generation of new knowledge by either validating or

challenging theoretical assumptions (85). The two frameworks that were used are the Consolidated Framework for Implementation Research (CFIR) of Damschroder *et al.* (2009) (86) and Kingdon's Multiple Streams Framework. The CFIR, although intended for the implementation of research findings and innovations into routine clinical practice, was selected as one of two frameworks for this research because its five domains are important for the implementation of complex interventions such as the AU Model Law and it can also be used to determine the perceived benefits, enabling factors and challenges encountered in the domestication and implementation of the AU Model Law (Objectives 1-3). The CFIR therefore served as the conceptual and analytical framework for gaining a comprehensive understanding of the implementation of the AU Model Law in AU Member States whereas Kingdon's Multiple Streams Framework informed data analysis by framing the empirical results in a theoretical context when examining the agenda setting process leading to the ratification of the AMA treaty using Burkina Faso, Ghana, Mali, Rwanda, and Seychelles as case studies. Furthermore, these two theoretical frameworks were incorporated to the research to specify which key variables influence the phenomena of interest and to examine how these key variables differed and under what circumstances (85). The two theoretical frameworks will be applied to different parts of the methods (i.e., analysis only or instrument development and analysis) to meet each of the research objectives. The rationale for this is explained later on.

3.7.1 The Consolidated Framework for Implementation Research

The foundation of the Consolidated Framework for Implementation Research (CFIR) of Damschroder *et al.* (2009) (86) is a previous synthesis of implementation factors carried out by Greenhalgh *et al.* (2004) using snowball sampling for the identification of new theories. The CFIR is a meta-theoretical framework that provides a menu of constructs associated with effective implementation and includes taxonomy, terminology and definitions that create a knowledge base of implementation factors across multiple contexts (86). The CFIR identifies constructs across five domains for individuals involved with the process of implementation to consider. These domains include:

- Intervention Characteristics - includes eight constructs related to characteristics of the intervention being implemented into a particular organisation;
- Outer Setting - includes four constructs related to factors such as the economic, political and social context within which an organisation resides;
- Inner Setting - includes 12 constructs related to features such as the structural, political and cultural contexts through which the implementation process will proceed;
- Characteristics of Individuals - includes five constructs related to the individuals involved with the intervention and/or implementation process; and
- Process - includes eight constructs related to essential activities of the implementation process that are common across organisational change models.

Figure 7 illustrates the CFIR and its main domains.

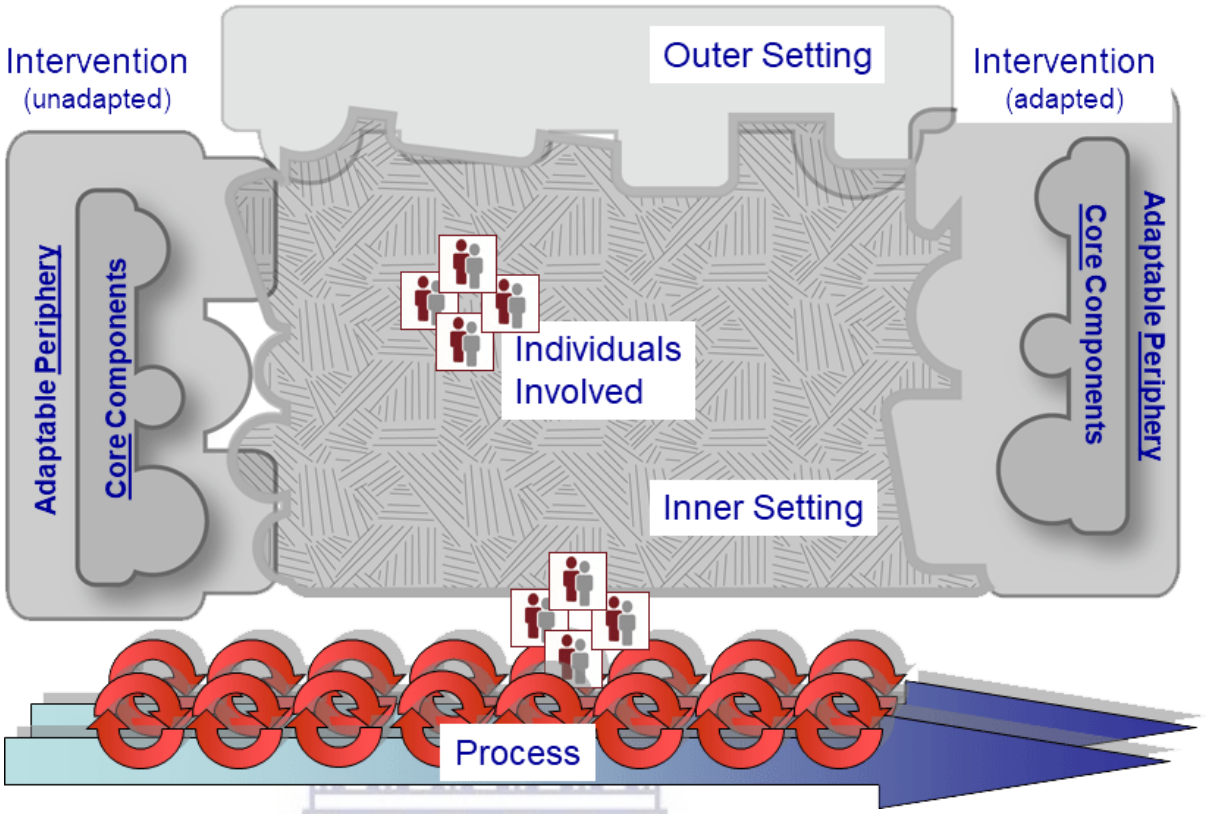

Figure 6: The Consolidated Framework for Implementation Research (CFIR) of Damschroder et al (87).

The CFIR, by providing a framework of constructs, promotes consistent use of constructs, systematic analysis and the organisation of findings from implementation studies (87). The CFIR can also be easily adapted to suit diverse settings and scenarios, including low-income contexts (87). In addition, the CFIR provides a practical approach for the systematic assessment of facilitators and potential barriers encountered in the implementation of an innovation (87).

3.7.2 The Multiple Streams Framework of John Kingdon

John W. Kingdon proposed a framework for understanding public policy agenda setting within the fragmented political system of the USA using first hand and secondary examinations of the agenda processes (88,89). Kingdon's Multiple Streams Framework, which was inspired by the 'garbage can' model (90), organises social issues based on theory which can result in changes in relevant policy or the creation of new policies (89). It addresses why and how certain issues become defined as problems while others do not, as well as why certain

proposed solutions receive more attention and become agenda items while others do not. The framework identifies people and groups that influence government agendas and the processes by which they do so (89,91).

The explanation offered by Kingdon on how agenda setting works focuses on three streams: problem, policy, and politics (88,89,92).

- Problem Stream: the problem stream refers to the process of convincing policy decision makers to pay attention to one problem over another (89,91). Before something becomes defined by someone as a problem, it is simply a condition. The difference between a condition and a problem is that problems are considered to be something we ought to do something about (89). For a condition to become a problem, it often violates social norms, values and points of view. Conditions can also become problems when circumstances are compared with those observed or reported elsewhere (89,91,93).
- Policy Stream: the policy stream has the outputs of experts and analysts who examine problems and propose solutions (88). It is also in this stream where alternative solutions to a policy are generated (89,91,94). The numerous possibilities for policy action or inaction are identified, assessed, and narrowed down to a few feasible options (88). The policy proposals need to find a problem to become coupled to and also have considerable support in order to take priority on the agenda. For a policy proposal to survive, it must fulfil certain criteria such as technical feasibility, public acceptance and reasonable cost (89).
- Politics Stream: factors that have an impact on the body politic such as swings in the national mood, executive or legislative turnover, and interest group advocacy campaigns make up the politics stream (88,89). In essence, for an item to have a high priority on the agenda the political mood must be right (89).

These three streams are generally independent, flowing along different channels, governed by their own rules and processes which have an impact on the movement of events on the agenda (88,91). These three streams do not

necessarily follow each other in a sequential or logical order (91). However, at specific critical points in time, these separate streams cross and a 'policy window' opens (88,89,91,94). Problems are then coupled to solutions, and both are joined to favourable political forces resulting in an issue getting recognition as a problem on the official or institutional agenda, and the public policy process then begins to address it (88–90). Policy change can only occur when all three streams come together and if the streams do not cross, the policy change will either not occur or be considerably difficult to obtain (90,92,94). The coupling of problems to solutions, and both of these to political opportunities is done by 'policy entrepreneurs'. Policy entrepreneurs are people who invest their resources in advocating for their pet proposals or problems, and prompt important people to pay attention. They have a critical role to play in shaping the course of the three streams and with tenacity, knowledge and power, they attempt to further their own policy aims in government's agenda in order to solve specific problems (88,89,94). The opening of policy windows, which occurs quite infrequently, can be triggered by seemingly unrelated external focusing events such as crises, accidents or the presence (or lack thereof) of policy entrepreneurs both within and outside of governments (88,89). The policy windows can also be opened by institutionalised events such as elections or deadlines (88,89). Additionally, the opening of a policy window can trigger the opening of another policy window elsewhere in a related area. This is the 'spill over' concept (89,90). A summary of Kingdon's framework is portrayed in Figure 8.

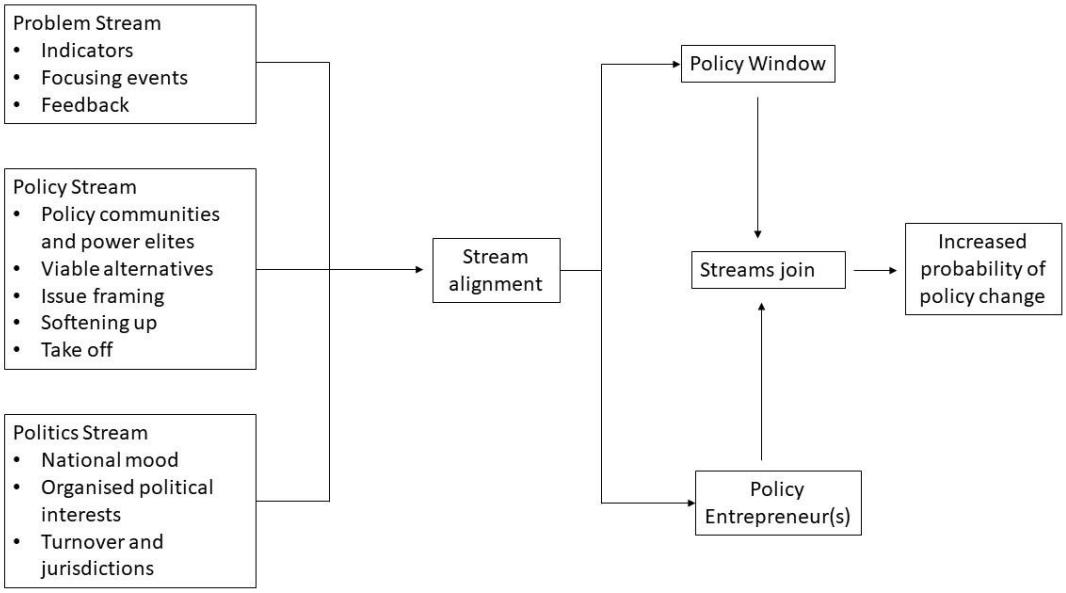

Figure 7: Kingdon's Multiple Streams Framework.

3.8 Summary

This literature review first looked at NMRAs in general and then focused on NMRAs in Africa. Global medicines regulatory harmonisation initiatives were also reviewed. These include the ICH, EMA as well as other medicines regulatory harmonisation collaborations. Furthermore, literature on the harmonisation of medical product regulations in Africa and harmonisation in regional economic communities was reviewed. This literature review also looked at capacity building through Regional Centres of Regulatory Excellence, the perspectives of the pharmaceutical industry regarding medicine registration processes and regulatory harmonisation initiatives, as well as the potential benefits and challenges of regulatory harmonisation in Africa. Lastly, literature on the African Union Model Law on Medical Products Regulation and on the African Medicines Agency was reviewed. It is hoped that this research study will add to the body of knowledge on the foregoing. The next chapter will describe the methodology that was used in this research study.

CHAPTER THREE

METHODOLOGY

3.1 Introduction

This chapter presents the methodology that was used in this study. The methods are described in two parts. Part I, section 3.2, details the methods for the census survey on the domestication and implementation of the AU Model Law on Medical Products Regulation and the signing of the treaty for the establishment of the African Medicines Agency. In this part, a description of the study design is provided, as well as the study area and population, sampling strategy and selection criteria, recruitment strategy and data collection, the measuring instrument, pre-testing the instrument, validity and reliability of the instrument, rigour, and data analysis.

Part II, section 3.3, describes the methods for the qualitative semi-structured interviews that were done to gain an understanding of the agenda setting process leading to the ratification of the AMA treaty in AU Member States selected as case studies. Part II therefore outlines the study design, study area and population, sampling strategy and selection criteria, the recruitment strategy and data collection, measuring instrument, familiarisation, and data analysis.

This chapter ends by discussing ethical considerations for the research study as a whole.

3.2 The Domestication and Implementation of the AU Model Law on Medical Products Regulation and the Signing of the Treaty for the Establishment of the African Medicines Agency

3.2.1 Study Design

Research study design refers to a framework, or set of methods and processes, that is used to collect and analyse data on variables that have been specified in a specific research problem (95). There are several different types of research study designs and each has its own advantages and disadvantages (95). Taking into consideration this study's research questions and their nature, this study was a cross-sectional survey based on primarily qualitative research methods with some

quantitative elements. A cross-sectional survey design was selected as it has several advantages. These advantages include the fact that surveys are flexible, they can be used with many populations, and attrition is less of a concern with cross-sectional surveys compared to when a longitudinal survey is used (96).

Quantitative research is the “the numerical representation and manipulation of observations for the purpose of describing and explaining the phenomena that these observations reflect," whereas qualitative research refers to "the non-numerical examination and interpretation of observations, for the purpose of discovering underlying meanings and patterns of relationships" (97). This research study employed a qualitative approach. There is a misconception that ‘qualitative’ insinuates that processes and meanings are not examined or measured rigorously, if measured at all, in terms of amount, quantity, frequency or intensity (97). Qualitative researchers emphasise the socially constructed nature of reality, the intimate relationship that exists between what is studied and the researcher, and situational constraints that influence inquiry (97). Qualitative studies are therefore useful when attempting to gain an in-depth understanding of participants’ lived experiences, the significance of those experiences, as well as the phenomenon that the experiences illustrate (98). On the other hand, quantitative studies stress the measurement and analysis of causal relationships that exist between variables instead of between processes and inquiry is claimed to be within a value-free framework (97).

Both deductive and inductive approaches can be applied to either quantitative research methods or qualitative research methods, however quantitative research methods are more often associated with deductive approaches and qualitative research methods are more often associated with inductive approaches. Deductive research begins with a known theory and it seeks to test it whereas inductive research begins by making observations to either develop a new hypothesis or to contribute to new theory (97). Another difference between quantitative and qualitative research is that the former is often linked to the belief of “science as objective truth or fact”, whereas the latter is more often identified with the view that “science is lived experience and therefore subjectively determined” (97).

Moreover, quantitative research tends to start with pre-specified objectives that focus on testing preconceived outcomes whereas qualitative research often starts with open-ended observation and analysis which usually look for patterns and processes that explain "how and why" questions (97).

In this research study, qualitative research methods were used due to our belief that the broad range of questions that we sought to answer are best addressed this way. It was our contention that the use of qualitative research methods within this research study could offer a richer and deeper understanding of the domestication and implementation of the AU Model Law on Medical Products Regulation and the signing of the AMA treaty by AU Member States than would otherwise be possible.

3.2.2 Study Area and Population

This study was carried out remotely from the University of the Western Cape in South Africa and the study area consisted of 45 African jurisdictions: 22 were Francophone (Algeria, Benin, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo Brazzaville, Cote D'Ivoire, the Democratic Republic of Congo, Gabon, Guinea, Madagascar, Mali, Mauritania, Morocco, Niger, Senegal, Togo, and Tunisia) and 23 were Anglophone (Botswana, Egypt, Eritrea, Ethiopia, The Gambia, Ghana, Kenya, Lesotho, Liberia, Namibia, Nigeria, Seychelles, Sierra Leone, Somalia, South Africa, Sudan, South Sudan, the Kingdom of Eswatini, (mainland) Tanzania, Tanzania (Zanzibar), Uganda, Zambia, and Zimbabwe).

The study population consisted of Heads of NMRAs of AU Member States and their Chief Regulatory Officers (or an alternative senior competent person). The Heads of NMRAs and Chief Regulatory Officers were selected due to their favourable positioning in the NMRAs to know about the status of domestication and implementation of the AU Model Law and the signing of the AMA treaty. Furthermore, they could provide information on the motivation (or lack thereof), enabling factors, challenges/barriers, and internal processes related to AU Model Law domestication and implementation as well as AMA treaty signing and ratification.

3.2.3 Sampling Strategy and Selection Criteria

There are two types of surveys: census surveys and sample surveys. This research study conducted a census survey. A census collects information from all units of the population, whereas a sample survey only collects information from a fraction of units of a population (99). However, using the information collected, both types of surveys involve calculating statistics for the population as a whole, and in some cases for subgroups of the population (99). In this study, purposive sampling was used. Information was sought from 45 African NMRAs, and two individuals from each NMRA were requested to complete the questionnaires. The list of all 55 AU Member States is Appendix I of this document. One advantage of conducting a census is that it has no sampling error due to all members of the population being enumerated. However, all surveys can have errors unrelated to sampling (non-sampling errors), and these errors may lead to biased survey results (99).

3.2.3.1 Inclusion criteria

Eligible countries were Anglophone and Francophone AU Member States. From these countries, eligible participants were the Heads of NMRAs and Chief Regulatory Officers (or an alternative senior competent person who would be selected by the Head of the NMRA).

3.2.3.2 Exclusion criteria

Lusophone AU Member States (Angola, Guinea-Bissau, Mozambique, and São Tomé and Príncipe) were excluded from the survey due to lack of capacity to translate the questionnaires and respondents' responses from English to Portuguese and vice versa. Equatorial Guinea was also excluded due to Spanish and Portuguese being the official languages.

Countries that do not actively participate in the African Medicines Regulatory Harmonisation (AMRH) initiative were also excluded from the study as the contact details for their Head of NMRA or a designated focal point person were not available in the AUDA-NEPAD AMRH database. These countries are Djibouti, Libya, Malawi, Mauritius, and Sahrawi Republic.

Rwanda was excluded from the main survey as the research instruments for Part I of this research study were piloted on the Rwanda Food and Drugs Authority. Rwanda will, however, be included in Part II of the study, i.e., the study on the agenda setting process leading to the ratification of the AMA treaty, as it was the first African country to sign, ratify and deposit the ratification instrument. It therefore offers important lessons. No pilot study was done for Part II due to a small sample size; only five countries met the inclusion criteria. The inclusion criteria is elaborated on in section 3.3 of this thesis.

3.2.4 Recruitment strategy and data collection

Before commencing the study, ethics clearance was obtained from the University of the Western Cape HSSREC (HSSREC Reference Number: HS21/5/39). After it was approved, the email addresses of Heads of African NMRAs were obtained from the AUDA-NEPAD and emails were sent to the Heads of NMRAs informing them of the aims, objectives, and procedures of the research. Permission was also obtained from the NMRAs for the respondents to participate in the study. In addition, the Heads of NMRAs and Chief Regulatory Officers (or another senior competent person) gave consent to participate in the study. The emails contained an introductory letter and consent forms to participate in the study (Appendix II). The email also contained a Survey Monkey link which enabled participants to complete the self-administered questionnaires (Appendix III and IV). Depending on the official language spoken in the recipient's country, the email, questionnaires, and the accompanying documents were in English or French. Two bilingual healthcare professionals (a medical doctor and a pharmacist) independently translated the questionnaires from English to French and sent these to the researcher who served as the language coordinator. The translators were briefed on what they are translating in order for them to know as much as possible about the study and context and translate accurately. The translation exercise aimed to achieve 'pragmatic equivalence' in translation instead of 'semantic or conceptual equivalence'. Pragmatic equivalence "aims to have the same *effect* in the target language reader as the original would have in the source language reader" (100). The language coordinator compared the translations and discussed any apparent discrepancies with the translators who

provided their rationales for the choices they made. After the discussion and agreement on items, a final version of the questionnaire was developed and used in this research study. Participants were given six weeks to complete and submit the questionnaires (26 October 2021 – 10 November 2021), and reminder emails with the Survey Monkey link were sent out at the start of week 3, 4, 5 and 6. When any of the questionnaire responses were unclear, respondents were contacted by email to clarify their responses. As the survey involved high-level participants, AMRH initiative staff at the AUDA-NEPAD were engaged to support this research and facilitate access to NMRAs in the data collection phase.

3.2.5 Measuring Instrument

Self-administered questionnaires were developed with both closed and open-ended statements (Appendix III and IV), and responses from these questionnaires were analysed as quantitative and qualitative data respectively. Self-administered questionnaires were chosen as the measuring instrument because they allow large numbers of completed questionnaires to be collected in a very short period of time and at low costs (101). They also allowed our high-level respondents scattered across the African continent to decide where and when the questionnaires would be completed (101). Additionally, respondents can take as long as they need to complete the questionnaires, consult other NMRA staff for certain sections of the questionnaires (if necessary), and provide the well-considered responses needed (101). Furthermore, a list of email addresses of respondents was available to send the questionnaires to. Lastly, having an interviewer present was not desired as it can influence responses and introduce unwanted interviewer effects (101).

Consisting of 26 questions, the self-administered questionnaire (Appendix III) sought to address specific country-level aspects that influence the domestication and implementation of the AU Model Law. It had questions that can be grouped into rationale and motivation for AU Model Law domestication and implementation, AU Model Law domestication and implementation enabling factors, and AU Model Law domestication and implementation challenges. Appendix IV is also a self-administered questionnaire, and it consists of 17

questions that seek to address specific country-level aspects which influence the signing and ratification of the treaty for the establishment of the AMA.

3.2.6 Pre-testing the instrument

The research instruments were pre-tested in one conveniently sampled AU Member State (i.e., Rwanda) where the Director General of the Rwanda FDA and the Head of the Drugs and Food Assessment and Registration Department were requested to each complete the questionnaires. Permission was obtained from the Rwanda FDA to allow the respondents to respond to the questionnaire. One AU Member State was used for pre-testing due to the small study population available. These participants are not part of the main survey, and the following was obtained from them:

a) Clarity of questions

b) Length of the questionnaire

c) Time required to complete the questionnaire

d) Method of administering the questionnaire

When asked how clear and easy to understand the questions were, the pilot study participant responded 90/100 for Questionnaire I and 100/100 for Questionnaire II. The justifications for these ratings are that *"as a person who initiated the review of the Rwanda FDA law and aligning with the provisions of the model law, it was clear to me"* and *"The questions were very clear. I have been the champion for the AMA in Rwanda and I have participated in the drafting/discussions of the AMA treaty"*, respectively. The pilot study participant was also asked if there were any important questions that had been omitted that they thought should have been included in the questionnaires and they responded *"No"*. Additionally, the participant reported that the length of the questionnaire was "*fair*" as they did not take long to complete it. SurveyMonkey was also found to be user friendly and easy to use as the participant scored it 95/100. No comments about the questionnaire or areas for improvement were provided by the pilot study participant. Based on these findings, we proceeded to conduct the research study as we had found that the right NMRA staff had been identified to

participate in the study, the questions were clear, the questionnaire had a reasonable length and did not take long to complete, and SurveyMonkey was a good data collection tool.

3.2.7 Validity and reliability of the instrument

Validity and reliability are important considerations in questionnaire design. Validity refers to the degree to which an instrument measures that which it claims to measure (102). There are several validity tests that have been developed and they include face validity, construct validity, content validity and criterion validity. This research used content validity to ascertain the degree to which the measuring instrument fully assesses or measures the construct of interest (102). To achieve a content valid instrument, a rational analysis of the instrument is typically done by experts familiar with the construct of interest or experts on the research subject (102). Therefore, regulatory affairs and policy professionals from the IFPMA African Regulatory Network and Temple University reviewed all the questionnaire items for clarity, comprehensiveness, and readability. An agreement was then reached on which items should be included in the final research questionnaire.

Reliability is the degree to which a questionnaire, test, observation or any measurement procedure generates the same results on repeated trials (102). Although reliability contributes to the validity of a questionnaire, it is not a sufficient condition for a questionnaire's validity. Divergence between observers or measuring instruments, or instability of the attributes being measured can result in a lack of reliability and subsequently affect the validity of the questionnaire. Therefore, reliability has three aspects: equivalence, stability, and internal consistency/homogeneity (102). Although it is difficult to design a reliable questionnaire, one can be developed that approaches a consistent response level (102). In this research, we sought to obtain a high reliability of response by wording questions in a way that reduces bias.

Further, validity and reliability were enhanced by conducting a pilot test. This was a precautionary step to ensure that each item on the questionnaire is clear and easily understood by respondents and the interpretation of each item is being done

in the intended manner. The questionnaire items also have an intuitive relationship to the research topic.

3.2.8 Rigour

According to literature, a crucial aspect of qualitative research methods is rigour and it is used to ensure the quality of research findings. As a result, several strategies have been put forward by scholars to ensure the trustworthiness of qualitative research findings. These strategies used as criteria for rigour in this research were identified and explained below.

3.2.8.1 Credibility

Credibility refers to the ability to ensure that the research study measures what it is meant to measure (103). In this study, several strategies were used to ensure credibility. Firstly, a literature review was conducted prior to data collection and it identified the enabling factors, processes, benefits and challenges of pharmaceutical policy implementation and medicines regulatory harmonisation. This was then used to ascertain whether the enabling factors, processes, (real and perceived) benefits and challenges described by the study participants were similar to previous research (103).

According to literature, credibility can also be ensured through obtaining an honest account of events from participants (103). Therefore, this research employed several strategies to ensure that the participants' accounts were true. For example, voluntary and informed consent as described in the section of this thesis on Ethical Considerations was obtained from participants as a means of ensuring credibility. Obtaining voluntary and informed consent ensured that data was collected from participants who were genuinely willing to participate in this research and were therefore more likely to give honest accounts of their experiences with AU Model Law domestication and implementation as well as AMA treaty signing and ratification. Furthermore, it was made clear to the participants that the researcher was not affiliated to AUDA-NEPAD, or the African Union, and the responses provided would be de-identified. This enabled open and honest responses to be provided on the questionnaires.

3.2.8.2 Audit trail

Audit of decision trails is performed to enable the reader to reach their own decisions about the quality, transferability and worthiness of a study (104). The authors' decision trail may then be followed by the reader who associates it with their own conclusions drawn from the information provided. Literature states that an audit of the decision trail involves providing a detailed description of sources and techniques of data collection and analysis, interpretations made, decisions taken, and influences on the researcher with the aim of demonstrating truthfulness within the findings (104). This was done in this study to ensure rigour.

3.2.8.3 Peer debriefing

Peer debriefing is also known as "analytic triangulation". It is a method in which the researcher discusses the research methodology, data analysis and interpretations continuously throughout the research process with their peer who is not directly involved in the research project (104). The peer debriefer should be someone who can pose meaningful questions to the researcher about their interpretations, provoke critical thinking, and offer alternative or additional explanations and perspectives (104). The credibility and trustworthiness of the research study is enhanced by peer debriefing as it gives the researcher a chance to ensure that emergent hypotheses, themes or theories are derived from the data, make sense and are plausible to a disinterested debriefer (104). In this study, the researcher's supervisors acted as debriefers (104) and frequent meetings were held throughout the study for the researcher to report back any issues in the research as well as to seek guidance from his supervisors based on their experiences and perceptions (103). Other forms of peer debriefing done in this research include the student presenting his research findings at conferences and presenting preliminary findings to interested groups (104), in this case the regulatory affairs and policy professionals from the IFPMA African Regulatory Network and Temple University.

3.2.8.4 Thick description

External validity (transferability) is obtained by providing rich and thick descriptions. This promotes study credibility. Thick description requires the

researcher to give sufficient details about the study settings, inclusion and exclusion criteria, sample characteristics, and data collection and analysis methods in order for the reader to evaluate the extent to which the conclusions made by the authors are transferable to other settings, situations, and populations (104). This was done in this research study as a detailed description of the study methodology, including study design, data collection, data analysis, and theory informing the methodology was included in this thesis to enable the reader to assess transferability.

3.2.9 Data analysis

The process of data analysis involves summarising data collected and interpreting its meaning in a manner that provides clear answers to research questions (99). As part of data analysis for this study, the questionnaire responses were downloaded from Survey Monkey, and each submitted questionnaire was subjected to either open coding or *a priori* coding, and then thematic analysis.

There are two approaches that can be used to code data. These are emergent coding where codes are drawn from the text (open coding) and *a priori* coding where codes are generated beforehand and applied to the text (105). Emergent coding aims to identify the meaning within a text without any preconceptions whereas *a priori* coding makes use of a purposefully developed framework as a means to draw out meaning (105). Open coding can be done in different ways. For instance, Glaser (1978, 1992) suggests that open coding should be done line by line whereas Corbin and Strauss (1990) encourage coding "conceptually similar events/actions/interactions" (105). Glaser (1978) also proposes “constant comparisons of data and categories” whilst Corbin and Strauss (1990) suggest that "the research process itself guides the researcher" (105). In this part of the research study, both open coding and *a priori* coding were applied and they were based on concepts instead of line by line as the latter is considered by some scholars to be rather arbitrary in that font size used and the length of the line (rather than the quality of the data) determines the amount of data on each line. One of the issues that have been identified with using open coding is that “the process implies that there is an actual truth out there awaiting discovery and that

by coding and recoding [researchers] should be able to find this truth" (105). It has also been asked whether any coding system can really be "open" as researchers are all independently positioned subjects that are likely to begin any activity with a certain point of view which might be called "individual perspective", "practitioner insight", "experience", "common sense", "institutional guidance" or "theory" (105).

When applying open coding, individual participant responses were firstly coded for emergent key words and the data was allowed to "speak for itself". Afterwards, repetitions of codes were sought and drawn together. Codes that had substantial overlaps were then merged and coded aspects were analysed for sub-themes. This process led to the development of codes that were drawn and refined, and the codes were then revisited to highlight relevant areas of data. Not all data from the texts being analysed fit neatly into codes and this did not mean that such data was not important. Therefore, to classify the data in as much detail as possible, all texts were analysed three times. Lastly, key themes or theory were identified and other codes were arranged around central concepts. The data was manually coded using highlighter pens as opposed to using computer software such as NVivo. Manual coding was selected due to personal preference and unlike computer software, it did not require time to become proficient in using it. The possibility of having a second and third researcher coding the data was also considered as a means of addressing subjectivity. However, the researcher coded and analysed all the data as there is limited guidance on how researchers can work collaboratively to develop inter-coding groups (105). There is also no clear evidence that the inter-coding of qualitative data is dependable and can improve the validity of the developed codes (105). Instead, validity of the codes generated was ensured by constantly establishing "causal inference that would best capture the data's imageric meaning" (105).

Thematic analysis is a type of qualitative analysis that is used to analyse classifications and present themes (patterns) that relate to the data. It was selected as the method of analysis in this study as it illustrates data in great detail and deals with diverse subjects via interpretations (106). Thematic analysis also provides a

systematic element to data analysis and allows the researcher to associate an analysis of the frequency of a theme with one of the whole content (106). This confers accuracy and intricacy, and enhances the research's whole meaning (106). Additionally, thematic analysis enables researchers to precisely determine the relationships between concepts and compare them with the replicated data. Thematic analysis therefore presents an opportunity to link various concepts and opinions of the study participants and compare these with data generated in different situations at different times during the research study (106). Furthermore, the flexibility of thematic analysis makes it suitable for data interpretation, deductive and inductive approaches, as well as coding and categorising data into themes (106).

Analysis may be inductive or deductive. Inductive analysis is when codes arise from the data in an open coding process and deductive analysis is when predetermined categories are used. Deductive analysis was done using the Consolidated Framework for Implementation Research (CFIR) of Damschroder *et al.* (2009) (86) which served as the conceptual and analytical framework for gaining a comprehensive understanding of the implementation of the AU Model Law in AU Member States. Although intended for the implementation of research findings and innovations into routine clinical practice, the CFIR was selected as one of two frameworks for this research because its five domains are important for the implementation of complex interventions such as the AU Model Law and it can also be used to determine the perceived benefits, enabling factors and challenges encountered in the domestication and implementation of the AU Model Law (Objectives 1-3). Inductive analysis was then done to address Objectives 4 – 5 which focus on the signing of the treaty for the establishment of the AMA.

Although this is a qualitative study, there were a few variables that were quantitative in nature. These data were summarised using descriptive statistics in Microsoft Excel and presented as bar charts and pie charts.

3.3 The Agenda Setting Process Leading to the Ratification of the Treaty for the Establishment of the African Medicines Agency

3.3.1 Study design

A qualitative case study scrutinises a particular phenomenon "within its real-life context" with the particular purpose of understanding something that is unique to that case (107). With case studies, the collected data is related to a specific individual, group, or event. However, several events or cases may be studied (107). The knowledge gained from the case study is then applied to other cases and/or contexts. Often, qualitative case study methods involve several in-depth interviews over a certain period with each case. Compared to a typical phenomenological interview, these interviews interrogate the case's unique aspects in great detail (107). A case study approach for qualitative data collection and analysis has several implications including having to select participants and/or cases based on their unique properties, having generally small sample sizes because of the interest in the case's unique properties, as well as focusing mainly on the defining features of the case and the differences that are exhibited from other individuals and/or events in the rest of the population (107). The aim is to investigate what makes the case, individual, group, or event different and why, and to apply the knowledge obtained from the case study to a larger population (107). Based on these reasons and factors, a case study design was used to conduct this section of the research.

3.3.2 Study area and population

This study was carried out remotely from the University of the Western Cape in South Africa and the study area consisted of Burkina Faso, Ghana, Mali, Rwanda, and Seychelles. These countries had ratified the AMA treaty by September 2020. The study population consisted of key informants with known involvement in the process of signing and ratifying the treaty for the establishment of the African Medicines Agency in the 5 AU Member States that were used as case studies. . An overview of the study area is presented in Table 4.

Table 4: Overview of the study area.

AU Member State	NMRA	Population Size[1] (2020)	Economic Classification[2]
Burkina Faso	Direction Générale de la Pharmacie, du Médicament et des Laboratoires	20,903,273	Low-income
Ghana	Food and Drugs Authority	31,072,940	Lower-middle income
Mali	Direction de la Pharmacie et des Médicaments, Ministre de la Sante et de l'Hygiene Publique; MoH	20,250,833	Low-income
Rwanda	Rwanda Food and Drugs Authority	12,952,218	Low-income
Seychelles	Medicine Regulatory Unit, Public Health Authority	98,347	High-income

[1] African Countries by Population. https://www.worldometers.info/population/countries-in-africa-by-population/

[2] For the current 2023 fiscal year, low-income economies are defined as those with a Gross National Income (GNI) per capita, calculated using the World Bank Atlas method, of $1,085 or less in 2021; lower middle-income economies are those with a GNI per capita between $1,086 and $4,255; upper middle-income economies are those with a GNI per capita between $4,256 and $13,205; high-income economies are those with a GNI per capita of $13,205 or more. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups

3.3.3 Sampling strategy and selection criteria

Recruitment of key informants was based on their involvement in the process of signing and ratification of the AMA treaty in the 5 AU Member States that were used as case studies. Involvement was determined and verified by reviewing press releases published on the African Union website about AU Member States that

have signed and/or ratified and national media briefings as well as contacting the NMRA staff of the country to confirm the informant's involvement. Key informants were drawn from NMRAs, Ministries of Health, government, and the AUC. The key informants were recruited using snowball sampling and permission was obtained from the AUC and relevant authorities in the 5 AU Member States for the key informants to participate in the study. Snowball sampling is a popular sampling method in qualitative research and it typically involves researchers starting with a small number of initial contacts (seeds) who fit the research criteria being invited to participate in the research (108). The agreeable participants are then requested to recommend other contacts who fit the research criteria and who may also be keen to participate in the research, and they in turn recommend other potential participants, and so on (108). Therefore, researchers use their networks to establish initial links and sampling momentum will develop from these, capturing an increasing chain of participants (108). Sampling will usually end when a target sample size or a point of saturation is reached. In this research study, snowball sampling was used due to its networking characteristics and flexibility which is particularly important when seeking hard-to-reach populations, populations with low numbers, geographically dispersed participants, and participants who require a degree of trust in order to become a willing participant (108). Snowball sampling has its shortcomings and it has been criticised for its selection bias as well as lack of external validity, generalisability and representativeness (108). The snowball can also fail to roll when using snowball sampling, i.e. the researchers can fail to recruit new participants due to a lack of recommendations or a lack of willing participants (108).

3.3.4 Recruitment strategy and data collection

An introductory letter highlighting the aims, objectives, and procedures of the research as well as a copy of the interview questions (Appendix V) was sent via email to the potential key informants in December 2021. The snowball sampling began with experts at the African Union Commission as their contact details are available in the public domain. Appointments were made for one-on-one in-depth qualitative semi-structured interviews to be held between 3 January 2022 and 31 March 2022. Semi-structured interviews are the most commonly used interview

technique in qualitative research and in a healthcare context (109). The reason for its frequent use is its flexibility and versatility, and it can be combined with both individual and group interview methods (109). It was selected as the data collection method in this research study as it enables reciprocity between the interviewer and the key informant (109). Semi-structured interviews also enable the interviewer to ask follow-up questions based on the key informant's responses and it allows space for key informants' individual verbal expressions (109). One-on-one interviews were done remotely using video-conferencing platforms convenient for the participants e.g., Google Meets, Zoom, or Microsoft Teams. Participants were verbally consented at the start of the interview and permission to record the interview was also requested. Interviews were recorded and transcribed verbatim. The interview transcript was then sent to the key informant to check it before the data was analysed. This process is referred to as member checking, respondent validation, or participant validation.

Within this qualitative research, the researcher was both the data collector and data analyst which could potentially result in researcher bias (110). The voice of the qualitative researcher might dominate that of the participant in the research due to the researcher imposing their personal beliefs and interests on all the research process stages (110). The potential for researcher bias might, however, be minimised through the active involvement of the research participant in checking and confirming the results. The method of returning an interview or analysed data to a participant is member checking, and it is used to validate, verify, or assess the trustworthiness of qualitative results (110). Member checking also enables researchers to ensure the accurate portrayal of participant voices by allowing participants the opportunity to confirm or deny the accuracy and interpretations of data (98). This adds credibility to the qualitative study (98). Additionally, the purpose of member checking is to encourage an alternate interpretation. It has been reported that often participants will not acknowledge the member checking request from the researcher; however, in instances where participants have agreed to participate in the member checking process, research has been improved upon (98).

There are a number of ways in which member checking can be conducted. For example, it can be done by returning an interview transcript to participants, having a member check interview using the interview transcript data or interpreted data, a member check focus group, or returning analysed synthesised data (110). In this research study, member checking was done by returning the interview transcript to participants in order for them to check the accuracy of the account. This method was selected as it is appropriate for checking factual information, it enables the addition of new data, and it enables participants to reconstruct their narrative through deleting extracts that they consider to no longer represent their experience (110). The interview transcripts were also returned relatively quickly (within a week of the interview) to participants so that they can review them while the interview is still fresh in their memory. Although this method enables researchers to make claims about the interview transcripts being accurate, it does not enable claims to be made about the trustworthiness of subsequent analyses (110). Additionally, member checking may not help with the validity of the study due to the power dynamic that exists between the researcher and the participant. Participants may simply agree with the contents of the transcripts as they perceive the researcher as having power and they do not want to disagree with them (98).

Key informants were given two weeks to conduct member checking of the transcripts and if no feedback was provided, the data analysis proceeded using the available information. This is because, ethically, after a follow-up email or reminder letter, researchers must accept that the participant does not wish to be further involved in the research study (110). Personal information of participants was de-identified. This means that information that identifies participants or can be used or manipulated by any foreseeable method to identify participants or can be linked by foreseeable methods to other information that identifies participants, was deleted.

3.3.5 Measuring instrument

An interview guide (Appendix V) was developed to conduct one-on-one in-depth qualitative semi-structured interviews with the identified key informants.

Kingdon's Multiple Streams Framework was used to develop the interview questions. The rationale for this is that the framework, which was inspired by the 'garbage can' model (90), organises social issues based on theory which can result in changes in relevant policy or the creation of new policies (89). The framework also addresses why and how certain issues become defined as problems while others do not, as well as why certain proposed solutions receive more attention and become agenda items while others do not. Moreover, the framework identifies people and groups that influence government agendas and the processes by which they do so (89,91). Therefore, it enabled the researcher to develop an interview guide that contains the important questions that must be asked and considered about the agenda setting process for treaty ratification.

3.3.6 Familiarisation

All the interviews were conducted and transcribed by the researcher and this enabled him to become familiar with the data. To become more familiar with the data, the researcher then repeatedly read the transcripts.

3.3.7 Data analysis

The interviews were transcribed verbatim in Microsoft Word, which was also used to manually organise and analyse the data. *A priori* coding and deductive analysis were used to gain an understanding of participants' responses. The coding involved looking for the motivation to ratify the AMA treaty, as well as the enabling factors, challenges, ratification processes, agenda setting events, windows of opportunity, and the policy entrepreneurs involved. Coded segments of the transcripts were retrieved and further analysed for recurrent or conflicting patterns. Coded segments were categorised according to Kingdon's Multiple Streams Framework which informed this data analysis, framing the empirical results in a theoretical context when examining the agenda setting process leading to the ratification of the AMA treaty using Burkina Faso, Ghana, Mali, Rwanda, and Seychelles as case studies (Objective 5). This examination of the agenda setting process was intended to contribute important lessons for countries attempting to sign and ratify the treaty.

The initial data analysis was performed by the student, and his supervisors performed a second analysis of transcripts. A comparison of findings was then done and any differences in interpretations were resolved through discussion.

3.4 Ethical Considerations

In line with the Protection of Personal Information Act (POPIA), researchers in this study have the responsibility to ensure that all personal information is processed in a manner that complies with the Act, i.e., all processing of personal information will be done on a lawful basis and as necessary solely for research purposes. All information was collected directly from the participants and with informed consent. All participants were given consent forms to sign before completing the questionnaires. The consent forms were accompanied by a covering letter that explains the aims, objectives, methods and demands on the participants. Participants were informed about why the information was being collected, who was collecting it, where it was being held, and their rights to access, delete or correct the data. Participants were free to leave any questions unanswered and could withdraw from the study at any stage. For this study, no data or personal information was transferred to other parties in South Africa or to foreign jurisdictions during processing. Personal information of participants was de-identified. This means that information that identifies participants or can be used or manipulated by any foreseeable method to identify participants or can be linked by foreseeable methods to other information that identifies participants, was deleted. The consent form is included as Appendix II in this thesis.

3.5 Summary

A detailed description of the methodology used in this study was provided in this chapter. Part I provided a description of the methods for the census survey on the domestication and implementation of the AU Model Law on Medical Products Regulation and the signing of the treaty for the establishment of the African Medicines Agency. In this part, a description of the study design was provided, as well as the study area and population, sampling strategy and selection criteria, recruitment strategy and data collection, the measuring instrument, pre-testing the instrument, as well as validity and reliability of the instrument. Data was

analysed using both inductive and deductive approaches. Part II described the methods for the qualitative semi-structured interviews that were done to gain an understanding of the agenda setting process leading to the ratification of the AMA treaty in AU Member States selected as case studies. This section outlined the study design, study area and population, sampling strategy and selection criteria, the recruitment strategy and data collection, measuring instrument, and familiarisation. Data analysis involved *a priori* coding and deductive analysis. Rigour and ethical considerations were maintained throughout the study. The next chapter will discuss the results of the study.

CHAPTER FOUR

RESULTS

4.1 Introduction

This chapter presents the findings of this research study. For the purpose of clarity, the results of this thesis will be presented in three parts: Part Ia – The domestication and implementation of the African Union Model Law on Medical Products Regulation addresses Objectives 1 - 3; Part Ib – The signing and ratification of the treaty for the establishment of the African Medicines Agency addresses Objective 4-5; and Part II – The agenda setting process leading to the ratification of the treaty for the establishment of the African Medicines Agency addresses Objective 6.

4.2 Part Ia – The domestication and implementation of the African Union Model Law on Medical Products Regulation

Twenty-six completed questionnaires were received from 21 NMRAs. The research target was 90 completed questionnaires from 45 NMRAs. 69.2% (n=18) of these completed questionnaires were from NMRAs in Anglophone countries (Botswana, Ethiopia, Ghana, Kenya, the Kingdom of Eswatini, Liberia, Namibia, Seychelles, Sierra Leone, South Sudan, Tanzania (mainland), Tanzania (Zanzibar), The Gambia, and Zimbabwe) and the remaining 30.8% (n=8) of the questionnaires were from NMRAs in Francophone countries (Burundi, Cape Verde, Comoros Islands, Ivory Coast, Niger, Togo, and Tunisia). No responses were received from Algeria, Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Congo Republic, Democratic Republic of Congo, Egypt, Equatorial Guinea, Eritrea, Gabon, Guinea, Lesotho, Madagascar, Mali, Mauritania, Morocco, Nigeria, Senegal, Somalia, South Africa, Sudan, Uganda, and Zambia. This study therefore had 47% of the NMRAs participating in the research and a 28.9% response rate from the participating officials.

All the countries in this study have an NMRA or an administrative unit that is responsible for the regulation of medical products. 95.2% of the NMRAs that participated in this survey (n=20) stated that there is legislation in place for

medicines regulation. One country (Seychelles) does not have legislation for medicines regulation. In some countries, legislation for medicines regulation dates back as far as 1957 whereas in other countries, legislation first came into effect as recently as 2020. Most countries have updated their legislation at least once and some are currently doing so. Table 5 provides an overview of legislation for medicines regulation in AU Member States that have domesticated the AU Model Law and Table 6 provides an overview of legislation for medicines regulation in AU Member States that have not yet domesticated the model law. This study found that countries update their legislation for medicines regulation for reasons such as the desire to establish a new regulatory authority, to transform the existing regulatory authority, or to align their legislation with the AU Model Law and international best practices. 33.3% (n=7) of NMRAs reported that they have domesticated the AU Model Law and 92.9% (n=13) of the countries that have not domesticated the model law stated that despite having not domesticated the model law, they have an intention to do so. Only one NMRA indicated that they have no interest in domesticating the model law as their law, which came into effect a few years before the model law was developed, already had all the components of the AU model law.

Table 5: Legislation for Medicines Regulation in 6 African Union Member States that have Domesticated the AU Model Law (N=6).

AU Member State	NMRA	Title of Legislation	The year when legislation first come into effect	The year when the legislation was last updated
Burundi	Autorité Burundaise de Régulation des Médicaments à usage humain et des Aliments (ABREMA)	Loi N°1/11 du 8 Mai 2020 portant réglementation de l'exercice de la pharmacie et du médicament à usage humain	2020	Not applicable as legislation recently came into effect
Cote d'Ivoire	Autorité Ivoirienne de Régulation Pharmaceutique (AIRP)	Loi 2017-541 du 03 Aout 2017	-	2017
Kenya	Pharmacy and Poisons Board	The Pharmacy and Poisons Board Act, CAP 244	1957	2019
Tanzania (mainland)	Tanzania Medicines and Medical Devices Authority	Tanzania Medicines and Medical Devices Act , CAP 219	2003	2019
Tanzania (Zanzibar)	Zanzibar Food and Drug Agency (ZFDA)	Zanzibar Food, Drug And Cosmetics Act #2/06 and its Amendment #3/17	2007	2017
The Gambia	Medicines Control Agency	Medicines and Related Products Regulations 2020	2015	2020
Tunisia	Direction de la Pharmacie et du Médicament	Loi 85-91 réglementant la fabrication et l'enregistrement des médicaments humains Loi 78-23 relative à la pharmacie vétérinaire	1969	2020

ABREMA, Autorité Burundaise de Régulation des Médicaments à usage humain et des Aliments; AIRP, Autorité Ivoirienne de Régulation Pharmaceutique; ZFDA, Zanzibar Food and Drug Agency (ZFDA).

[a] Process currently at the level of the Ministry of Health.
[b] Food and Medicine Regulation, Proclamation 112/2019 is a recently revised regulation in April 2019. The oldest regulations were Proclamation 199/1999 and then 661/2010.
[c] Ghana is currently in the process of domesticating the model law.

[d] Legislation was last updated in 2020; however, current amendments to the Act are yet to be endorsed.

[e] The revision of the 1997 law is in progress. This revision considers the domestication of the model law.

[f] It has been updated but not yet approved in 2021 to address current emerging issues in tandem with the AU model law.

Table 6: Legislation for Medicines Regulation in African Union Member States that have not Domesticated the AU Model Law (N=14).

AU Member State	NMRA	Title of Legislation	The year when legislation first come into effect	The year when the legislation was last updated
Botswana	Botswana Medicines Regulatory Authority (BoMRA)	Medicines and Related Substance Act of 2013	2013	Amendment of the Act is ongoing
Cape Verde	Entidade Reguladora Independente da Saúde (ERIS)	Decreto - lei nº 59/2006 de 26 de décembre, que réglemente l'autorisation de mise sur le marché, l'enregistrement, la fabrication, l'importation, la commercialisation et le publicité de médicaments à usage humain	1993	2006
Comoros[a]	Agence Nationale des Médicaments et des Evacuations Sanitaires (ANAMEV)	Code de la Santé Publique, Livre V	1995	2020
Ethiopia	Ethiopian Food and Drug Authority	Food and Medicine Regulation, Proclamation 1112/ 2019	1999	2019[b]
Ghana[c]	Food and Drugs Authority	Public Health Act, 2012 (ACT 851) - Part 7	1992	2012
Kingdom of Eswatini	Ministry of Health – Medicines Regulatory Unit (MoH-MRU)	Medicines and Related Substances Control Act No. 9 of 2016	2016	2020[d]
Liberia	Liberia Medicines and Health Products Regulatory Authority	An Act to Establish the Liberia Medicines and Health Products Regulatory Authority (LMHRA) of 2010	2010	N/A
Namibia	Namibia Medicines Regulatory Council	Medicines and Related Substances Control Act, Act 13 of 2003	2003	2007

Niger[e]	Direction de la Pharmacie et de la Médecine Traditionnelle	Loi N°97-05 du 02 Juin 1997 Portant Ratification de l'Ordonnance 97-05 Portant Législation Pharmaceutique	1997	2021
Seychelles	Medicine Regulatory Unit, Public Health Authority	Not applicable	Not applicable	Not applicable
Sierra Leone	Pharmacy Board of Sierra Leone	Pharmacy and Drugs Act 2001	1988	2001[f]
South Sudan	South Sudan Drug and Food Control Authority	South Sudan Drug and Food Control Authority Act 2012	2012	Not yet updated
Togo	Direction de la Pharmacie, du Médicament et des Laboratoires (DPML)	Loi n° 2009-007 du 15 mai 2009 portant code de la Santé Publique de la République togolaise. (Titre IV : du médicament, des dispositifs médicaux et de la pharmacie)	2009	Not yet updated
Zimbabwe	Medicines Control Authority of Zimbabwe	Medicines and Allied Substances Control Act 15:03	1969	1997

ANAMEV, Agence Nationale des Médicaments et des Evacuations Sanitaires; BoMRA, Botswana Medicines Regulatory Authority; DPML, Direction de la Pharmacie, du Médicament et des Laboratoires; ERIS, Entidade Reguladora Independente da Saúde; LMHRA, Liberia Medicines and Health Products Regulatory Authority; MoH-MRU, Ministry of Health – Medicines Regulatory Unit.

[a] Process currently at the level of the Ministry of Health.

[b] Food and Medicine Regulation, Proclamation 112/2019 is a recently revised regulation in April 2019. The oldest regulations were Proclamation 199/1999 and then 661/2010.

[c] Ghana is currently in the process of domesticating the model law.

[d] Legislation was last updated in 2020; however, current amendments to the Act are yet to be endorsed.

[e] The revision of the 1997 law is in progress. This revision considers the domestication of the model law.

[f] It has been updated but not yet approved in 2021 to address current emerging issues in tandem with the AU model law.

The results for this section of the thesis (i.e., Part I) will be organised according to the five domains of the Consolidated Framework for Implementation Research (CFIR). The five domains are intervention characteristics, outer setting, inner setting, characteristics of individuals, and process.

4.2.1 Intervention characteristics

The constructs under intervention characteristics are intervention source, evidence strength and quality, relative advantage, adaptability, trialability, complexity, design quality and packaging, and cost.

The following constructs were not brought up by survey respondents:

- Intervention source refers to the perception of key stakeholders about whether the intervention is externally or internally developed.
- Relative advantage is stakeholders' perception of the advantage of implementing the intervention versus an alternative solution.
- Trialability is the ability to evaluate the intervention on a small scale in the organisation, and to be able to reverse course (undo implementation) if warranted.
- Design quality and packaging refers to the perceived excellence in how the intervention is bundled, presented, and assembled.
- Cost refers to the costs of the intervention and costs associated with implementing the intervention including investment, supply, and opportunity costs.

4.2.1.1 Evidence strength and quality

This construct deals with stakeholders' perceptions of the quality and validity of evidence supporting the belief that the intervention will have desired outcomes.

In this research study, 34.6% (n=9) of the respondents consider the harmonisation of regulatory systems and enabling cooperation with other NMRAs to be a benefit of domesticating and implementing the model law. One respondent stated that "*aligning with the AU model law will make regional and continental*

harmonisation easier. Since the AU Model Law is comprehensive, it ensures that all aspects of medicines regulation and control are covered. It may also facilitate mutual recognition between and amongst countries" (P5). Other participants shared the same sentiments as they stated that the model law was expected to "*fill the gaps in the current Act as well as to allow regional harmonisation*" (P17), "*support harmonisation of the data requirements for evidence of quality, safety, and efficacy of medical products across the sub-region*" (P8), and to bring about a "*wider scope of regulated products, and alignment to regional and international laws that would enable harmonisation initiatives*" (P10).

Other common perceived benefits of domesticating the model law include being "*in line with regional international standards and best practices*" (P4), "*facilitating the exchange of regulatory information*" (P6), "*an increased number of registered medical products*" (P6), "*improving the regulation of medical products and technologies*" (P8), curbing the circulation of substandard, falsified, and illicit medical products, and having an NMRA that is "*fully mandated to conduct regulatory activities*" (P15). One participant (P15) felt that domesticating and implementing the model law would also enable the regulated community to clearly understand their roles.

In addition, the model law's domestication and implementation was perceived by respondents to result in a strong, autonomous regulatory authority (P22), "*improve transparency and efficiency of the medicines regulatory framework and safety monitoring systems*" (P8) and enable countries to have appropriate laws that include all regulatory functions expected of a national medicines regulatory authority (P21). This ensures that medicines distributed in countries are safe, efficacious and of good quality. For countries with limited resources, it was expressed that the "*AU Model Law was timely as it enabled [them] to adopt strong pharmaceutical laws in a rapid manner*" (P21).

Furthermore, one participant perceived the model law "*to outline and put regulations in proper perspectives*" (P2), i.e., it would "*expand policies, result in a coordinated approach for medicines regulation, enable the evaluation of incoherent policy frameworks, and enable efficient and aligned frameworks to be*

developed" (P2). A participant from a different country considered domestication and implementation to result in "*better oversight of clinical trials, increased export opportunities for domestic pharmaceutical manufacturers, increased confidence in the health system and medicines, and reduced antimicrobial resistance*" (P11).

Moreover, one participant voiced that for them, being the first country in the region to domesticate the AU model law was considered beneficial as it would bring attention to their NMRA and enable them to participate in regional and continental harmonisation initiatives (P7). Another participant thought that AU model law domestication would allow them to "*participate in the realisation of the African Medicines Agency project*" (P22).

Stakeholders' perceptions of the quality and validity of evidence supporting the belief that the intervention will have desired outcomes are corroborated by 7 NMRAs in 6 African countries that have implemented the AU Model Law who report that they are accruing benefits from implementation. The benefits accrued are perceptions as no objective data was submitted. Table 7 highlights the reported benefits of implementing the AU Model Law. These include enabling the establishment of an NMRA, improving NMRA governance and decision-making autonomy, strengthening the institutional framework, having streamlined activities which attract support from donors, as well as enabling harmonisation, reliance, and mutual recognition mechanisms.

All participants who stated that they have implemented the AU Model Law reported that there have been no disadvantages to its implementation.

Table 7: The benefits of AU Model Law implementation reported by 7 African NMRAs (N=9).

Participant	AU Member State	Benefits Accrued from AU Model Law Implementation
P22	Tunisia	The participant had no benefits to report at this stage.
P23	Cote d'Ivoire	1. Better governance 2. Management autonomy, decision-making autonomy 3. Strengthening of the institutional framework
P21	Burundi	1. Creation of ABREMA with clear missions for each service allowing the smooth running of regulatory functions 2. With the pricing of services, not yet in place, ABREMA will have financial resources allowing it to implement its mission 3. The pharmaceutical sector is well regulated 4. The reduction of dependence on technical and financial partners in the regulations
P10	Kenya	1. Increased revenue streams 2. It has enabled harmonisation, reliance, and mutual recognition mechanisms
P12	Kenya	1. Cooperation with other regional, continental, and international institutions therefore saving time taken to make regulatory decisions 2. Provided a framework for improving regulation of medicines

		3. Transparency and accountability increase as the functions and powers of the NMRA are clearly stipulated in law 4. Effective governance of the NMRA as the CEO is appointed by the Board
P26	Kingdom of Eswatini	1. The provisions on making use of regulatory decisions made in other jurisdictions have been of particular benefit to Eswatini as a country with limited regulatory capacity
P9	Tanzania (mainland)	1. Alignment of the regulatory activities with other agencies and international organisations such as WHO 2. Having streamlined activities which attract support from donors 3. It has led to adequate systems for ensuring the quality, safety, and efficacy of medicines, medical devices, and other health technologies
P7	Tanzania (Zanzibar)	1. Harmonisation initiatives in EAC, twinning programmes, joint regulatory activities 2. The AU model law strengthened ZFDA's regulatory functions
P4	The Gambia	1. Establishment and capacity building of the NMRA to perform regulatory activities
ABREMA, Autorité Burundaise de Régulation des Médicaments à usage humain et des Aliments; AU, African Union; CEO, Chief Executive Officer; EAC, East African Community; NMRA, National Medicines Regulatory Authority; WHO, World Health Organization; ZFDA, Zanzibar Food and Drug Agency.		

4.2.1.2 Adaptability

Adaptability is the degree to which an intervention can be adapted, tailored, refined, or reinvented to meet local needs.

The AU Model Law is adaptable as countries can either domesticate it partially or in full to meet their needs. 47.6% (n=10) of the NMRAs are reported to have domesticated or to be domesticating the AU Model Law in full. These are NMRAs of Botswana, Burundi, Cote d'Ivoire, the Kingdom of Eswatini, Liberia, Sierra Leone, Tanzania (mainland), The Gambia, Tunisia, and Zimbabwe. 38.1% (n=8) of the NMRAs are reported to have domesticated or to be domesticating the AU Model Law partially, and these are national regulators of Comoros Islands, Ghana, Kenya, Namibia, Niger, Seychelles, Tanzania (Zanzibar), and Togo. All of these countries' regulatory authorities are adopting the component that allows for international cooperation and harmonisation of regulation of medical products. The components least adopted are for the establishment of an administrative appeals committee and for scheduling, classification and control of medical products. The remaining 14.3% (n=3) of NMRAs are uncertain about which type of domestication they will conduct. Figure 9 shows the type of AU Model Law domestication performed or being performed by NMRAs in Africa and Figure 10 illustrates the components of the model law adopted by NMRAs performing a partial domestication.

According to participants, full domestication of the AU Model Law was or is being done for the reasons outlined below.

"Full domestication was chosen to close some of the gaps identified by the WHO GBT assessment and to clarify other provisions that were in the current Act after benchmarking with the AU model law" (P15).

"To harmonise the regulatory procedures of [our country] with those of the Member States of the African Union" (P21).

"This law meets our expectations in terms of pharmaceutical regulation" (P23).

"The AU Model Law was found to contain all the provisions that were seen as necessary for the regulation of medicinal products in the country. It was also

thought that aligning the country's legislation to the AU Model Law would make it easier to participate in regional harmonisation initiatives on the regulation of medicinal products" (P26).

"As it relates to medicines regulations; to provide a framework to guide, strengthen the regulatory environment for the delivery of quality, safe and efficacious medicines. To accelerate access to lifesaving interventions to improve health impact" (P2).

"To follow international best practice" (P11).

Reasons for partial domestication of the AU Model Law mentioned by the participants are outlined below.

"There was a need for enhanced regulatory harmonisation" (P18).

"[Our country] is implementing a partial domestication because most of the provisions in the Model Law are already covered in the Public Health Act" (P8).

"The rest of the regulatory functions existed before the domestication of the AU Model Law. The [NMRA] is an existing regulatory authority. Amendments served to align [the medicines legislation] to the AU model law and to widen the scope" (P10).

"The intention is to enact a more comprehensive legislation to deal with the regulation of health products and technologies" (P12).

"Currently, there are a lot of omissions and loopholes in the Act, and they can be addressed by the sections in the AU model law" (P17).

"We have a law in place; the partial implementation is to include the provisions that are missing and to make some more comprehensive" (P5).

"The domestication of the model law will make it possible to put in place an adequate framework for the circulation of medical products of safe and effective quality" (P20).

"[Our country] is too small to establish a National Medicine Regulatory Authority. Instead, a Medicine Regulatory Service will be established as a section under the Public Health Authority" (P13).

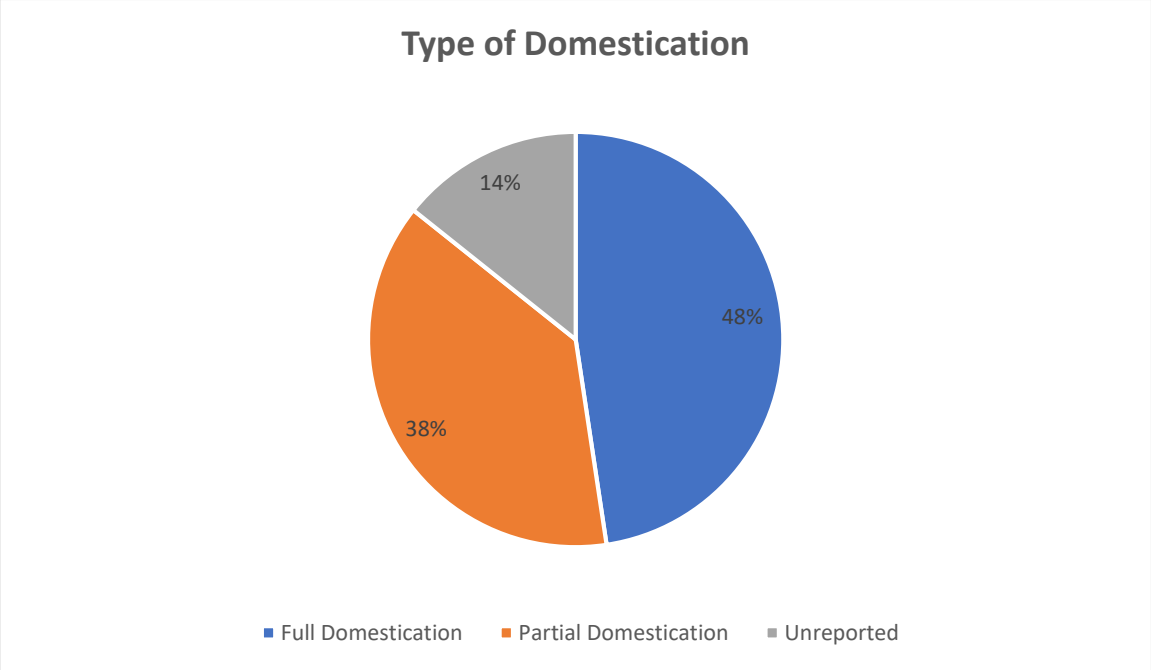

Figure 8: The type of AU Model Law Domestication performed or being performed by 21 African NMRAs (N=21)

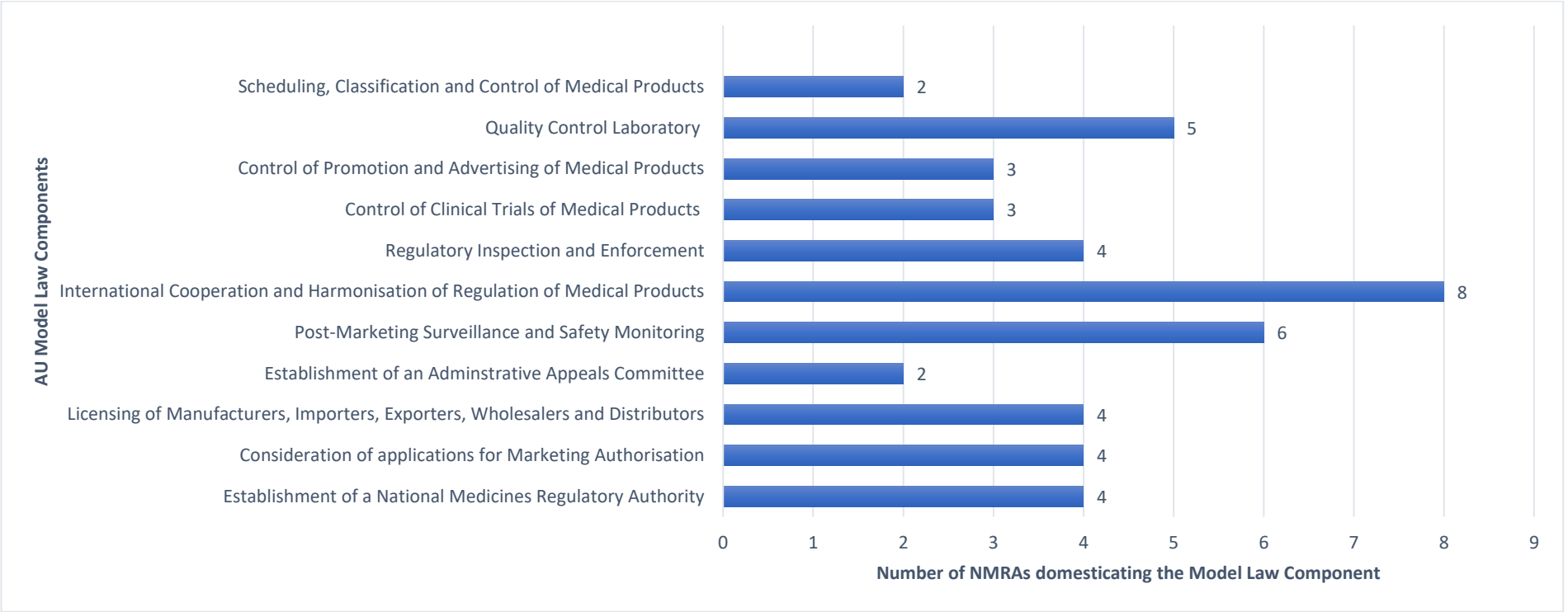

Figure 9: Components of the model law adopted or being adopted by the 8 African NMRAs performing a partial domestication (N=8).

4.2.1.3 Complexity

Complexity refers to the perceived difficulty of implementation, reflected by duration, scope, radicalness, disruptiveness, centrality, and intricacy and number of steps required to implement.

Most respondents stated that there were no perceived disadvantages of domesticating the model law. However, those that did considered the lengthy process of amending existing Acts to be a disadvantage. Participants also stated that model law domestication is a *"cumbersome process as change of legislation is onerous"* (P16) and *"amending laws is a slow process especially if there are no identified persons/institutions to push the agenda forward internally"* (P26).

In addition, one participant was concerned that *"since the provisions of the AU model law will be applied across the region, there is the possibility of [their country] relying on data from other member states by reason of harmonisation"* (P8) and the *"data might not be up to scratch"* (P8). Other perceived disadvantages that were reported include the fact that *"the expanded mandate [brought about by the AU model law] may not be affordable"* (P5) and *"regulated products are not common across the region, specifically the regulations for food"* (P10). It was also stated by a different participant that the AU model law *"does not address the issue of the management of unusable (expired) pharmaceutical products"* (P23) and it also *"does not address the question of other regulated products, in particular cosmetic products, dietetic products, food supplements, etc."* (P23).

Furthermore, the fact that *"the country should retain sovereignty in deciding what to regulate"* (P10) was considered a disadvantage of domesticating and implementing the model law.

4.2.2 Outer Setting

The constructs considered under the Outer Setting domain are patient needs and resources, cosmopolitanism, peer pressure, and external policy and incentives.

4.2.2.1 Patient needs and resources

This refers to the extent to which patient needs, as well as barriers and facilitators to meet those needs, are accurately known and prioritised by the organisation. This construct did not feature prominently when assessing the domestication and implementation of the AU Model Law.

4.2.2.2 Cosmopolitanism

Cosmopolitanism is the degree to which an organisation is networked with other external organisations.

In this research study, it was reported that *"participation in regional and international harmonisation programmes of different communities and development bodies, e.g. the EAC-MRH, WHO-PQ, WHO-CRP, Swissmedic etc."* (P21) enabled the domestication of the model law. This point is supported by another participant (P7) who stated that their NMRA's participation in the EAC medicines regulatory harmonisation initiative as per treaty and protocols of the establishment of the EAC was a facilitator of the domestication process.

4.2.2.3 Peer pressure

Peer pressure is mimetic or competitive pressure to implement an intervention typically because most or other key peer or competing organisations have already implemented or are in a bid for a competitive edge. This construct was not brought up by the study participants.

4.2.2.4 External policy and incentives

The external policy and incentives construct is a broad construct that includes external strategies to spread interventions, including policy and regulations (governmental or other central entity), external mandates, recommendations and guidelines, pay-for-performance, collaboratives, and public or benchmark reporting.

In several countries, the legislation for medicines regulation was updated due to the desire *"to align with the AU model law and provide for regulatory functions that were missing in the legislation"*. In addition to wanting to align with the AU Model Law, one country reported to be amending their legislation to close gaps

that were identified when their regulatory system was assessed using the WHO Global Benchmarking Tool (P14). Another country feels that they have an *"obligation to align with international recommendations"* (P22) and are therefore updating their legislation.

4.2.3 Inner Setting

The inner setting domain consists of the following constructs: structural characteristics, networks and communications, culture, implementation climate, and readiness for implementation. The following constructs were not consistent with our study findings:

- Structural characteristics refers to the social architecture, age, maturity, and size of an organisation.
- Networks and communications refer to the nature and quality of webs of social networks and the nature and quality of formal and informal communications within an organisation.
- Culture are the norms, values and basic assumptions of a given organisation.

4.2.3.1 Implementation Climate

Implementation climate is the absorptive capacity for change, shared receptivity of involved individuals to an intervention, and the extent to which use of that intervention will be rewarded, supported, and expected within their organisation. Implementation climate has the following six sub-constructs: tension for change, compatibility, relative priority, organisational incentives and rewards, goals and feedback, and learning climate.

1. Tension for change

Tension for change refers to the degree to which stakeholders perceive the current situation as intolerable or needing change.

I. The establishment of a new regulatory authority

One of the reasons why AU Member States were updating their legislation for medicines regulation is due to a desire to establish a new regulatory authority or restructure the existing one as the current authority (or the absence of one) was deemed to require changing. This point is supported by a francophone participant who stated that the motivation to update the legislation for medicines regulation in their country was due to the need for "*an autonomous and independent medicines regulatory authority for greater consumer protection against counterfeit, spurious or falsified pharmaceutical products and the illicit market"* (P23). Another respondent (P18) stated that the reason for updating the existing legislation in their country was political for their government which wanted to strengthen legislation and regulation of the pharmaceutical sector, as well as create a national medicine agency.

In African countries where a regulatory authority already exists, legislation was updated to transform the existing institution. For instance, in Ethiopia, the previous regulations were for all health products, professionals and services and all these were regulated by one Authority, the FMHACA. When the legislation was updated, it resulted in the Ethiopian Food and Drug Administration, a regulatory Authority with a mandate to regulate food and drugs. A similar situation occurred in Zimbabwe where the legislation was updated to change from the Drugs Control Council (DCC) and the Zimbabwe Regional Medicines Control Laboratory (ZRDCL) to the Medicines Control Authority of Zimbabwe (MCAZ) in 1997. In Ghana, *"the legislation was updated to provide for a more comprehensive law on public health, make the existing legislation more responsive to contemporary health issues and to upgrade the then Food and Drugs Board to a Food and Drugs Authority"* and in Tanzania, there was a desire to shift the regulation of food and cosmetics to the Tanzania Bureau of Standards, and the Tanzania Food and Drugs Authority (TFDA) became the Tanzania Medicines & Medical Devices Authority (TMDA).

II. Support for regulatory harmonisation and international collaboration

The desire to have legal provisions at the national level that allow regional harmonisation and international collaboration is one of the enabling factors that

featured prominently in this study. As one participant said, domesticating the model law is *"above all a question of the desire to have legal provisions which make it possible to protect public health through, in particular, regional harmonisation and international collaboration"* (P20) and another spoke of the *"need for harmonisation of pharmaceutical regulations"* (P23).

III. The desire to have an efficient and effective regulatory system

A participant stated that *"the desire to have an all-encompassing legislation for regulation of health products and technologies"* (P12) and *"the policy direction to set up a single regulatory authority for regulation of all health products and technologies"* (P12) were enabling factors for the domestication and implementation of the model law. This was supported by another participant that stated that model law adoption was enabled by *"the desire to strengthen legislation on medicines and health products on the African continent"* (P22). Additionally, in one country *"the regulatory framework is constantly being reinforced which has helped to domesticate the model law"* and in another, there is a *"breakthrough movement towards the achievement of [WHO] maturity level 3"* (P6). All these points illustrate the tension for change that must exist for implementation of interventions. Timing also enables model law domestication as one participant noted that in their country, *"it [the AU Model Law] came at the time the organisation was ready for amendments"* (P10). Furthermore, the presence of *"gaps in the current Act"* (P17) and the desire to *"have an appropriate law including all the regulatory functions of a national drug regulatory authority"* facilitated the adoption of the model law.

The rest of the sub-constructs do not fit with the findings of this study on the domestication and implementation of the AU Model Law:

- Compatibility is the degree of tangible fit between meaning and values attached to the intervention by involved individuals, how those align with individuals' own norms, values, and perceived risks and needs, and how the intervention fits with existing workflows and systems.

- Relative Priority refers to individuals' shared perception of the importance of the implementation within the organisation.
- Organisational Incentives and Rewards are extrinsic incentives such as goal-sharing awards, performance reviews, promotions, and raises in salary, and less tangible incentives such as increased stature or respect.
- Goals and Feedback is the degree to which goals are clearly communicated, acted upon, and fed back to staff, and alignment of that feedback with goals.
- Learning Climate is a climate in which: a) leaders express their own fallibility and need for team members' assistance and input; b) team members feel that they are essential, valued, and knowledgeable partners in the change process; c) individuals feel psychologically safe to try new methods; and d) there is sufficient time and space for reflective thinking and evaluation.

4.2.3.2 Readiness for Implementation

Readiness for implementation refers to tangible and immediate indicators of organisational commitment to its decision to implement an intervention. There are three sub-constructs under this construct, and these are leadership engagement, available resources, and access to knowledge and information.

1. Leadership Engagement

Leadership engagement refers to the commitment, involvement, and accountability of leaders and managers with the implementation. Political will and leadership are considered by the participants to be enabling factors for the domestication and implementation of the AU Model Law and one of them stated that they *"had the law already in place but needed some amendments. There was/is already political and senior leadership buy-in on the process"* (P5). Another participant reported that in her country, they had *"political support from our parent Ministry and the Government"* (P8). One participant attributed

successful domestication of the model law to *"goodwill from the management"* (P10) and *"the leadership of the CEO"* (P10).

2. Available Resources

Available resources refer to the level of resources dedicated for implementation and on-going operations, including money, training, education, physical space, and time.

The process of domesticating and implementing a law requires resources and participants stated that the availability of both financial and human resources enabled the process in their respective countries.

"Human and financial resources" (P11).

"At the national level, there are sufficient numbers of workforce and finance" (P6).

"Pharmacists in the public sector" (P13).

"Availability of human and financial resources" (P1 and P23).

3. Access to Knowledge and Information

This construct deals with the ease of access to digestible information and knowledge about the intervention and how to incorporate it into work tasks. Participants' responses cannot be assigned to this sub-construct.

4.2.4 Characteristics of Individuals

This domain has five constructs, namely knowledge and beliefs about the intervention, self-efficacy, individual stage of change, individual identification with organisation, and other personal attributes.

Participants' responses did not align with any of the constructs in this domain as defined below:

- Knowledge and beliefs about the intervention is individuals' attitudes toward and value placed on the intervention as well as familiarity with facts, truths and principles related to the intervention.

- Self-efficacy refers to individuals' belief in their own capabilities to execute courses of action to achieve implementation goals.
- Individual stage of change refers to characterisation of the phase an individual is in, as he or she progresses toward skilled, enthusiastic, and sustained use of the intervention.
- Individual identification with organisation is a broad construct related to how individuals perceive the organisation, and their relationship and degree of commitment with that organisation.
- Other personal attributes is a broad construct to include other personal traits such as tolerance of ambiguity, intellectual ability, motivation, values, competence, capacity, and learning style.

4.2.5 Process

The constructs in this domain are planning, engaging, executing, and reflecting and evaluating.

4.2.5.1 Planning

Planning is the degree to which a scheme or method of behaviour and tasks for implementing an intervention are developed in advance, and the quality of those schemes or methods. This construct does not align with the findings of this study.

4.2.5.2 Engaging

Engaging means attracting and involving appropriate individuals in the implementation and use of the intervention through a combined strategy of social marketing, education, role modelling, training, and other similar activities. There are four sub-constructs under engaging, and these are opinion leaders, formally appointed internal implementation leaders, champions, and external change agents. Definitions of these terms are as follows:

- Opinion leaders are individuals in an organisation who have formal or informal influence on the attitudes and beliefs of their colleagues with respect to implementing the intervention.

- Formally appointed internal implementation leaders are individuals from within the organisation who have been formally appointed with responsibility for implementing an intervention as coordinator, project manager, team leader, or another similar role.
- Champions are defined as "individuals who dedicate themselves to supporting, marketing, and 'driving through' an [implementation], overcoming indifference or resistance that the intervention may provoke in an organisation".
- External change agents are individuals who are affiliated with an outside entity who formally influence or facilitate intervention decisions in a desirable direction.

This research study found that one of the enabling factors for the domestication and implementation of the AU Model Law is the presence of advocates, facilitators, or champions for the cause. These can be either internal actors (i.e., NMRA staff) or external actors (i.e., persons who are not NMRA staff).

In terms of internal facilitators, champions, or advocates, 76.2% of the NMRAs (n=16) reported that they had internal facilitators in the process of AU Model Law domestication. Most of the internal facilitators were from the legal department/team, and they performed various roles. In one NMRA, the legal member of the NMRA *"facilitated the drafting of the layman draft"* (P17) and in another, *"the legal department facilitated the process and communicated with responsible government offices"* (P6). In addition, the NMRA's lawyer of one AU Member State is said to have worked with the Director, and *"through explanatory memoranda and meetings, they brought to the attention of the Authority the importance of domesticating such a law"* (P25). In another country, the legal team worked with the technical departments and identified implementation challenges and ensured that the process addresses them (P15). Lastly, the legal unit in of one NMRA captured *"all the new additions and ensured that the Medicines and Allied Substances Bill was submitted for review"* (P16).

The second most identified internal facilitators were technical staff of the NMRA who are said to have been instrumental in the drafting of the laws. For instance, one respondent highlighted that the NMRA technical staff played a role in the *"development of the amendment Bill and submission of comments in support of the Bill during the public participation stage of the Bill"* (P12). Technical staff also organised and participated in meetings as well as advocated for the domestication of the law to the Minister of Health, Cabinet and Parliament.

The Head of the NMRA as well as the Governing Board were also advocates for the domestication and implementation of the AU Model Law. One Head of Agency reported in the survey that they *"participated in member state committee and stakeholders' meetings as a representative of the NMRA and Ministry of Health (MOH)"* and another stated that they *"developed the draft law, presented in Board meetings, Ministry of Health, stakeholders' meeting, inter-ministerial Permanent Secretaries committee, AG chamber, Cabinet of Ministers and House of Representatives"* (P7). In one African country, the Governing Board, and the Head of the NMRA *"championed the domestication of the law through organising consultative stakeholder workshops and working groups to ensure that [the country's] Regulatory Health laws can effectively respond to contemporary health issues"* (P8). Other participants stated that their Heads of Agencies played a crucial advocacy role at the level of the Ministry of Health and *"monitored the drafting of the model law in accordance with the health code".*

The focal person for the regional medicines regulatory harmonisation initiative (P10) and the Public Health Commissioner of the country (P13) were also identified as internal facilitators of the process. In sum, *"having people that understand the importance of including the missing provisions in the national legislation"* (P26) is an important enabling factor for the domestication and implementation of the AU Model Law.

In terms of external facilitators, two thirds (n=14) of the NMRAs had external facilitators, advocates or champions involved in the AU Model Law domestication and implementation process.

The Ministry of Health was the most mentioned external facilitator in this process and its role differed from one country to the next. In some cases, it played the crucial role of *"communicating with the Attorney General and other government offices"* (P6) and submitting *"the bill to the office of the Attorney General and thereafter presenting their input during public participation"*. After the Ministry of Health, the most mentioned external facilitator was the AUDA-NEPAD which worked with RECs to raise awareness and engage political and senior leadership on the AU Model Law. The AUDA-NEPAD is also reported to have trained *"the actors involved in pharmaceutical regulation on this law and its implementation"* (P25).

Some countries had more external facilitators than others. One Anglophone and one Francophone country in particular stand out as they had support from several external institutions. The former listed the Ministry of Health, the AUDA-NEPAD and the WHO African Regional Office as external facilitators in their domestication process, and these actors *"provided technical and financial support in ensuring that [the country's] legislation on medicines aligns with the AU model law"* (P8). In the Francophone country, the Ministry of Public Health and the Fight against AIDS, the Ministry in charge of East African Community Affairs, the AUDA-NEPAD, the EAC, the World Bank, and the WHO country office were all external facilitators in the domestication and implementation process. Their roles were *"advocacy for the establishment of a Pharmaceutical Law based on the AU Model Law, financing meetings, and sensitising different institutions in the country"* (P21). One participant (P23) mentioned that in their country, WAEMU, the Agence Française de Développement (AFD), and WHO were external facilitators, and their roles were providing technical and financial support for the adoption of the AU Model Law.

Other less common external facilitators mentioned by study participants are the RECs (namely SADC and the EAC), WHO country offices, non-governmental organisations (P13), the local pharmaceutical industry (P10), and academia (P10).

4.2.5.3 Executing

Executing is carrying out or accomplishing the implementation according to plan.

I. The process of AU Model Law domestication and implementation

The process of domesticating the AU Model Law differs from one country to the next.

Most respondents indicated that in their country, the process of domesticating the model law begins with the NMRA's legal unit and the legal committee reviewing the existing legislation against the AU Model Law. Afterwards, the NMRA's legal unit and legal experts develop a draft law which is then reviewed by the Legal Committee. The draft law is then circulated to stakeholders for comments and final revisions are made by the NMRA's legal unit to incorporate any comments. The Legal Committee has the responsibility to approve the final draft law and it is then submitted to the Minister of Health for approval. Next, the draft law goes to the Attorney General's office for approval, and then to Cabinet, and finally to Parliament. If Parliament approves of the draft law, it is then published in the government gazette.

One participant stated a process that has less steps compared to other countries. For them, *"the Authority prepares a draft and then it is circulated to stakeholders who provide comments. Afterwards, the Board of the NMRA reviews a draft that has incorporated stakeholders' comments, and the Legal Committee then draft penalties, and the draft law goes to Parliament for approval"* (P2).

In one country, they circulate the Bill to stakeholders, both locally and regionally. This is done after the existing legislation is reviewed against the model law by the NMRA's Legal Committee and stakeholders from industry and professional groups and drafting instructions have been submitted to the Attorney General for drafting of the amendment Bill. Once the local and regional stakeholders have reviewed the draft law and provided their comments, it is submitted back to the Attorney General for final draft. This will be approved by Cabinet and then subjected to public comment. From there, it will be approved by Parliament and published in the gazette with effective commencement date. (P15)

In another country that has domesticated the model law, the NMRA's staff and the legal unit of the Ministry of Health reviewed the existing legislation against

the model law and then they drafted a Bill with the support of various partners. A high-level meeting was then organised by the EAC in the presence of other partners (i.e., the AUDA-NEPAD, WHO, and the World Bank) to advocate for the domestication of the AU Model Law. Next, the draft law was finalised by the legal team of the Ministry of Health and reviewed and approved by the National Service of Legislation (SNL). The draft law was then circulated to stakeholders for comments, after which final revisions were made to incorporate the comments. The SNL then approved the final draft, and the Bill was returned to the legal unit of the Ministry of Health. The draft law was then approved by the Minister of Health followed by the Council of Ministers. The Minister of Parliament then visited EAC countries that have set up NMRAs. Next, Parliament approved the draft law, and the law was promulgated by the President of the Republic. The last step was publication of the new law in the official gazette. (P21)

II. Challenges encountered in AU model law domestication and implementation

The challenges or barriers encountered in the process of domesticating and implementing the AU model law include the lack of human and financial resources, competing priorities at the national level, overlapping roles of government institutions, and the process of amending/repealing laws being slow and lengthy.

1. The lack of human and financial resources

26.9% (n=7) of participants stated that one of the challenges they encounter in adopting the model law is the lack of competent human resources. There is *"insufficient human resources in quality and quantity"* (P21), and in one country, there is *"inadequate funding and lack of competent human resources, especially pharmacists"* (P13).

As the model law can result in the establishment of a regulatory authority and the widening of the scope of regulatory functions, participants also stated that domestication of the model law causes *"resource constraints"* (P10) as *"more*

resources in terms of office space and human resources" (P10) are needed. Another participant stated that *"the functionality of the pharmaceutical regulatory agency once created can be a major challenge due to the lack of human resources in quantity and quality, and of the infrastructure to house the headquarters of the agency"* (P20).

2. Competing priorities at the national level

In some countries, there are competing priorities at the national level which impede the domestication and implementation of the model law. One participant stated that in their country, there were *"many concurrent legal reforms to align Acts with the new Constitution and Medicines and Allied Substances Control Bill did not make it top priority"* (P16).

Other challenges include the lack of *"political will and acceptance by the public"* (P2), *"lack of political will and resources to support legal reform"* (P11) as well as *"lack of prioritisation and availing of financial resources"* (P26).

3. Overlapping roles of government institutions

One participant (P7) reported that in their country, there is an overlap in legislation for the NMRA, Bureau of Standards, Chief Government Chemist, and for agriculture and livestock. Therefore, when the time came to adopt the model law, there were differing views regarding the AU Model Law components that should be domesticated and the types of products that the NMRA should regulate. In another country, a similar challenge emerged as there are *"overlapping missions in different texts"* (P21).

4. The process of amending/repealing laws is slow and lengthy

A participant explained that *"a key challenge is that the steps involved from drafting of the amendments to endorsement of the updated legislation involve different stakeholders. The urgency of moving forward with the process differs from stakeholder to stakeholder thus the process may not be as fast as may be desired by for instance the NMRA"* (P26). In one country, they stated that there is now *"blockage of the process at the level of the Ministry of Health"* (P19) and

in another there is "*misunderstanding of different ministries and government institutions"* (P21).

It is also difficult to have *"full engagement of stakeholders in a timely manner"* (P15) and as a result, *"consultations had to be extended several times to ensure inclusivity"* (P15).

III. Solutions to overcome the challenges encountered in domesticating and implementing the model law

To address the challenges encountered in AU Model Law domestication and implementation, NMRAs advocated for their governments and various stakeholders to adopt the model law, and they had frequent communication, consultations, and discussions on the importance of domestication of the AU Model Law. One participant stated that *"political will and resources are key and usually inadequate so more advocacy to governments especially Ministries of Health and Justice for the full domestication would greatly help"* and another said that they held *"stakeholders' consultations of political leaders including parliamentarian and Ministers of state on the importance of implementing the AU Model Law"* (P11). In addition, NMRAs requested assistance from development partners such as the World Bank, through the AUDA-NEPAD, the African Union, WHO, RECs and other international bodies. Furthermore, in countries where the AU Model Law's domestication was challenging due to overlaps in roles, duties, and responsibilities of the NMRA and another government institution, a solution that was being considered was *"the demarcation of roles, duties, and responsibilities"* (P7). In one country, the NMRA organised *"courtesy visits to exchange with the institutions concerned in order to understand the roles, responsibilities and limits of each"* (P21). NMRAs also sought funds to support the process (P17) and in cases where the process was slow and lengthy, timelines were extended to allow industry and stakeholders time to provide input (P15). One country with human resource challenges is advocating for the government to scale up the number of students who study pharmacy as well as to recruit more pharmacists (P13).

4.2.5.4 Reflecting and Evaluating

Reflecting and evaluating refers to quantitative and qualitative feedback about the progress and quality of implementation accompanied with regular personal and team debriefing about progress and experience. This construct did not align with the findings of this research study.

4.3 Part Ib – The signing and ratification of the treaty for the establishment of the African Medicines Agency

Twenty-six completed questionnaires were received from 21 NMRAs. The research target was 90 completed questionnaires from 45 NMRAs. 69.2% (n=18) of the completed questionnaires were from NMRAs in Anglophone countries (Botswana, Ethiopia, Ghana, Kenya, the Kingdom of Eswatini, Liberia, Namibia, Seychelles, Sierra Leone, South Sudan, Tanzania (mainland), Tanzania (Zanzibar), The Gambia, and Zimbabwe) and the remaining 30.8% (n=8) of the questionnaires were from NMRAs in Francophone countries (Burundi, Cape Verde, Comoros Islands, Ivory Coast, Niger, Togo, and Tunisia). No responses were received from Algeria, Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Congo Republic, Democratic Republic of Congo, Egypt, Equatorial Guinea, Eritrea, Gabon, Guinea, Lesotho, Madagascar, Mali, Mauritania, Morocco, Nigeria, Senegal, Somalia, South Africa, Sudan, Uganda, and Zambia. This study therefore had 47% of the NMRAs participating in the research and a 28.9% response rate from the participating officials.

At the time of this study, 55.0% (n=11) of the countries whose NMRAs participated in this research had signed the AMA treaty. Of these, 45.5% (n=5) had signed and ratified the AMA treaty. Overall, the treaty had not been ratified by 75% (n=15) of the countries whose NMRAs participated in this research. All the NMRAs in countries that had neither signed nor ratified the AMA treaty stated that their countries had an intention to do so. Each participating country's treaty signing and ratification status is presented in Table 8 below.

Table 8: The Status of Signing and Ratification of the AMA Treaty.

Countries that have not signed	**Countries that have signed but not ratified**	**Countries that have signed and ratified**
Botswana	Burundi	Ghana
Cape Verde	Cote d'Ivoire	Namibia
Comoros	Sierra Leone	Niger
Ethiopia	Tanzania	Seychelles
Kenya	Togo	Zimbabwe
Kingdom of Eswatini	Tunisia	
Liberia		
South Sudan		
The Gambia		

The results in this section are organised using the order of questions from the questionnaire and themes are introduced under each heading from the questionnaire.

4.3.1 The perceived advantages of the establishment of the African Medicines Agency

The AMA is perceived by the study participants to enable reliance and recognition mechanisms to be implemented by African NMRAs, enable access to medical products across the continent, improve regulatory systems across Africa, develop NMRAs' regulatory capacity and expertise, as well as to enable regulatory harmonisation on the continent.

1. The AMA will enable reliance and recognition mechanisms to be implemented by African NMRAs

There is a perception that the AMA will enable reliance and recognition mechanisms to be implemented by NMRAs in Africa. For instance, one respondent from a small country with limited regulatory capacity stated that for them, they anticipate to *"benefit a lot by relying on or recognising the regulatory work that will be done by AMA"* (P26).

2. The AMA will enable access to medical products in African countries

The AMA's establishment is also perceived to enable access to medical products in African countries. Participants stated that the establishment of the AMA is perceived to *"support market authorisation and improve quality of medicines distributed in the AU"* and *"facilitate access to safe, effective, good quality and affordable essential medicines and health technologies"* (P20), including biologicals and other complex molecules (P12). P5 believes that the AMA will *"serve as the advisory body for complex products"* and *"set the standards for medicinal and health product regulation on the continent"*. There is also a perception that the AMA's establishment will create employment opportunities and *"incentives for pharmaceutical manufacturers to set up their factories in African countries"* (P12).

3. The AMA will improve regulatory systems on the continent

Another theme that emerged is that the AMA's establishment is perceived to improve regulatory systems on the continent. One participant voiced that the AMA will *"enable [their country] to achieve acceptable international drug standards and provide a favourable regulatory environment for local production and marketing of pharmaceutical products"* (P25). Other perceived advantages of creating the AMA include that the AMA will govern regulations and *"improve the regulation of medical products and technologies"* (P8), result in *"more collaboration and support for countries with weak medicine regulatory systems"* (P13), create *"efficient regulatory authorities within the region"* (P17), *"strengthen pharmaceutical product control capacities"* (P20), and improve *"transparency and efficiency of the medicines regulatory framework and safety monitoring systems"* (P8).

4. The AMA will develop regulatory capacity and expertise of NMRAs

The AMA's establishment is perceived to result in the development of NMRAs' regulatory capacity and expertise. One participant stated that the *"establishment of AMA will provide some expertise that lack in our country especially as it is aimed at dealing with more complex applications"* (P15) and another responded that *"it [AMA] is a continental platform and will lead to improved regulation through capacity building to NMRAs and RECs"* (P10). There is a perception that

capacitation of countries with expertise will be *"due to the organised professional interaction"* (P12) that the AMA will foster. Countries also think that they will *"benefit from expert group discussions"* (P1) and the creation of centres of excellence (P23). Lastly, the AMA's creation is also thought to be advantageous due to the Agency gathering *"the rare expertise available in the region for assessment of specialised medicines such as vaccines"* (P9).

5. The AMA will enable regulatory harmonisation on the continent

Participants deem the establishment of the AMA to enable regulatory harmonisation in Africa. One participant stated that *"the advantages are that the harmonisation of the guidelines, procedures and technical requirements and professional experience will enhance quick and quality assessment and evaluation of medical products for registration and market authorisation"* (P3), a perception that several participants hold. In addition, participants stated that the AMA's establishment is an advantage as *"it will facilitate regulatory processes, the exchange of regulatory information and the harmonisation of regulatory processes"* (P6). It will also *"provide for harmonisation of the data requirements for evidence of quality, safety, and efficacy of medical products"* (P8), *"enhance the ease of doing business in African countries due to harmonisation initiatives"* (P12), and result in better control due to harmonisation of regulations and collaboration (P19). Furthermore, participants indicated that for them, the establishment of the AMA was perceived to result in pharmaceutical cooperation in the various regulatory functions (P23), pooling of technical resources (expertise and capabilities) disseminated across the continent for complex health products (P16), harmonised procedures, and regulations, as well as result in them being part of and benefitting from *"harmonisation initiatives and the business development plan"* (P4).

4.3.2 The perceived disadvantages of the establishment of the African Medicines Agency

80.8% of respondents (n=21) stated that in their country there were no perceived disadvantages to the establishment of the AMA. However, five respondents stated there were perceived disadvantages to the AMA's establishment. The first

respondent stated that if the AMA is operationalised, *"some duplication of effort may be present"* (P6) and the second respondent, from a different country, stated that *"the scope and mandate of AMA is ambiguous"* (P10) and there is a *"fear of the AMA taking up the roles of NMRAs"* (P10). Another participant mentioned that once the AMA is established and their country signs and ratifies, there will be a *"requirement for eventual financial contribution on the already overstretched country budget"* (P12). P5 believes that the AMA will result in *"loss of autonomy and revenue by national and regional authorities"*. Lastly, the fifth participant who had a perceived disadvantage to report stated that they *"have a concern whether countries with very limited regulatory capacity will have a voice or will have their needs catered for within the institution. One may find that the organisation continues to cater more for those with greater regulatory capacity and those with lower maturity level continue to be left behind"* (P26).

4.3.3 African NMRAs' expectations of the African Medicines Agency

The AMA is expected to be an information sharing agency, to improve access to medical products, strengthen and harmonise regulatory systems on the continent, assist countries establish NMRAs and build national regulatory capacity, and curb the circulation of substandard and falsified medical products in Africa. There is also an expectation that the AMA *"have a fair, transparent system and regional representativeness in the selection and appointment of experts/consultants"* (P16). The same participant further stated that there must be *"transparent good practices in reaching decisions on recommending products"* and *"independence from foreign governments and development partners with ulterior motives"* (P16). Furthermore, both respondents from one country (P10 and P12) stated that they expect the AMA to be hosted in their capital city and the AMA should be an agency that creates employment opportunities.

1. The AMA should be an information sharing agency

African NMRAs expect the AMA to be an information sharing agency. One participant mentioned that their NMRA expects to *"have the opportunity to enter the circuit of communication and exchange of information on medicines, between the African Medicines Agency, on the one hand, and the Regional Economic*

Communities, on the other hand" (P21). Other participants stated that they *"will require experience from other NMRA's through information exchange"* (P1) and expect there to be *"exchange of information on the quality, safety of all medical products including substandard and falsified medical products"* (P23). There is also an expectation that the AMA will *"regularly inspect, coordinate and share information about products that are authorised for marketing"* (P8).

2. The AMA should improve access to essential medical products

The AMA is expected to improve access to essential medical products as participants reported that *"the African Medicines Agency (AMA) is in an important position to leverage several regulatory assets and resources to improve access to essential medicines and safe, effective, quality and affordable health technologies"* (P24). They also expect the AMA to *"support market authorisation and improve quality of medicines distributed in the African Union"* (P13) and *"approve medical products in the event of a health emergency"* (P23). Furthermore, the continental regulator should *"provide advice on advanced therapies, such as biologicals, and the regulation thereof"* (P5).

3. The AMA should strengthen and harmonise regulatory systems on the continent

There is an expectation that the AMA be *"a strong organisation that can guide, support and strengthen regulatory structures"* (P4) in Africa and improve the regulation of medicines (P17). One participant stated that they expect to *"benefit from AMA's guidance on the systems for mobilising financial resources, human resources and all other resources in order to be able to properly regulate the pharmaceutical sector"* (P21) and another participant hopes that the "*AMA will serve as a continental body that will provide regulatory leadership to ensure the existence of harmonised and strengthened regulatory systems on the African continent"* (P24). Two other participants stated that they expect the AMA to *"join expertise together to strengthen medicines regulation systems in the NMRA, ultimately to provide access of good quality, safe and efficacious medicines to our population"* (P9) and *"to aid collaborations and harmonisation of medicines regulation and standards in Africa and different regions"* (P14). Harmonisation

is expected to result in products being placed on the market faster (P12) and the AMA should advance collaborative work and share expertise.

4. The AMA should assist countries establish NMRAs and build national regulatory capacity

The AMA is expected to support African countries in their endeavours to establish and operationalise their national medicines regulatory authorities (P20). It is also expected to result in *"more collaboration and support for countries with weak medicine regulatory systems"* while being *"fully visible and delivering as promised"* (P15). In addition, the AMA is expected to *"have a way of focusing on building the regulatory capacity of those member states with a lower maturity level"* (P26) and produce *"more positive energy towards the effectiveness of regulatory activities at national level"* (P6). Furthermore, *"capacity building of NMRA functions"* (P18) is expected to result from the AMA's creation and the continental regulator should aid and be involved in regulatory matters (P19). Moreover, the AMA is expected to *"engage NMRA staff and streamline the functions of NMRAs"* (P10).

5. The AMA should curb the circulation of substandard and falsified medical products in Africa

There is an expectation for the AMA to *"increase safety and quality of products continentally"* and the role that the AMA plays should *"complement the efforts of NMRAs in ensuring that the general public receives safe, quality and efficacious medical products and technologies"* (P8). In collaboration with NMRAs, the AMA is also expected to *"fight against the trade in counterfeit medical products"* (P8) and develop and implement a *"multi-faceted approach for combating SFs"* (P12).

4.3.4 Perceptions of African NMRAs' roles and contributions to/in the AMA

African NMRAs consider their role and contribution to/in the AMA to be to actively participate and be involved in all decisions (P20), to avail any support particularly the technical expertise needed to carry out the AMA's mission as

well as *"to share data and information"* (P8), including on substandard and falsified medical products. One participant stated that their NMRA *"will share its experience as a country with an established autonomous [regulatory] body"* (P1).

Additionally, NMRAs are keen to *"participate in strengthening pharmaceutical cooperation"* (P23) and to *"contribute by providing expertise in the different areas of medicines regulation, stimulating initiatives for the harmonisation of medicines regulation and contributing to the assurance of safe, effective and quality medicines on the continent"* (P24). Another participant perceived their NMRA's role to be to *"facilitate all the processes for effective implementation of the role and responsibilities of AMA"* (P6). Two participants (P7 and P22) from different countries mentioned that their contribution to/in the AMA will be based on successful participation in regional medicines regulatory harmonisation initiatives and being an active player in the establishment of harmonious regulations within the African continent.

NMRAs also perceive their role to be to contribute financially, if necessary (P21). In addition to the roles and contributions mentioned, one country's two respondents (P10 and P12) mentioned that theirs is also to host the agency in their capital city. There is also the hope that NMRAs would be *"consulted on the needs of member states with a lower maturity level"* (P26).

4.3.5 The process to sign and ratify the treaty for the establishment of the African Medicines Agency

The process to sign the treaty differs from one African Union Member State to the next. P12 stated that in their country, the general responsibility for treaty initiation is the National Executive and may be delegated to a relevant State Department. In this regard, the Cabinet Secretary responsible for Health is required to undertake public participation to seek and obtain the views of the public on the Treaty. The information presented below from a) to d) pertains to P12.

a) Approval by Cabinet

Upon undertaking public participation, the Cabinet Secretary (CS) responsible for Health, in consultation with the Attorney General, is required to submit the treaty to the Cabinet together with the accompanying memorandum.

b) Consideration by Parliament

Upon approval for ratification by Cabinet, the CS is required to submit the treaty and a memorandum on the same to the Speaker of the National Assembly. Parliament may approve the ratification with or without reservations to specific provisions of the treaty.

c) Approval for ratification

Where ratification is approved without any reservations to the treaty, the CS shall, within 30 days from the date of approval of the ratification of the treaty, request the Cabinet Secretary responsible for Foreign Affairs, to prepare the instrument of the ratification of the treaty. However, if there is approval with reservations, the treaty shall be ratified with those reservations to the corresponding article in the treaty. If it is refused by Parliament, the Government shall not ratify the treaty.

d) Ratification of the treaty

All instruments of ratification of a treaty shall be signed and deposited by the Cabinet Secretary responsible for Foreign Affairs at the African Union Commission and a copy thereof shall be filed with the Registrar of Treaties. The Ministry of Health in this country is obliged to take measures to inform and create awareness to the public about the effects and benefits of the treaty.

In another country, *"the NMRA wrote a concept note to the Minister of Health, who then has the responsibility of writing to the Minister of Foreign Affairs requesting the latter to submit a memo to the Council of Ministers to approve the process to sign and ratify the AMA treaty. The Minister of Justice then presents the request to the National Legislature for endorsement and approval"* (P3).

A different process described involves the treaty needing to *"first be signed by the President or an authorised representative of the President. The treaty must then be submitted to Parliament for ratification either by an Act of Parliament or*

by a resolution of Parliament supported by the votes of more than one half of all the members of Parliament. After this process is completed, the instrument of accession is deposited to the African Union Commission" (P8).

Another process reported starts with the Minister responsible for Foreign Affairs signing the treaty, after which the Minister of Health tables the treaty in Parliament and if it is approved, it is published in the government gazette and then implemented.

The process can also begin with the drafting of a concept note which is sent to the Ministry of Health for approval. The Ministry of Health then takes the matter to cabinet for discussion and development of a Cabinet Memo. Next, the Parliament endorses/ratifies the treaty, and the Cabinet Secretary Ministry of Foreign Affairs approves and forwards the ratification instrument to the African Union Commission. (P10)

Two participants (P13 and P26), both from small African states, stated that they were not sure of the process.

4.3.6 Facilitators, advocates, or champions in the process of signing and ratifying the AMA treaty

Facilitators, champions or advocates for the signing and ratification of the AMA treaty can either be internal, that is within the NMRA, or external.

55.0% (n=11) of countries reported that they had internal facilitators and 60.0% (n=12) reported that they had external facilitators. Some countries had both internal and external facilitators.

In terms of internal facilitators, the Head of the NMRA was cited the most along with the NMRA's Board. Their roles involved *"advocacy at the ministerial level"* (P19), *"spearheading the signing and ratification of the treaty"* (P8), as well as preparation of the Bill and explanatory memorandum/concept notes. For instance, P4 reported that they *"had been attending all conferences pertaining to the AU Model Law, the process of establishing the AMA and the African Medicines Regulatory Harmonisation programme"* (P3) and they *"compiled all information as a Concept Note to the Honourable Minister of Health and a copy to the*

Honourable Minister of Foreign Affairs and International Cooperation. From time to time, I have tried to persuade the Honourable Ministers to process the signing of the treaty and ratifying it. That is our responsibility and technical advice" (P3). Other internal facilitators include NMRA staff, including the legal departments and committees, pharmacists, and the Public Health Commissioner, the NMRA's focal person for the regional medicines regulatory harmonisation initiative, and the NMRA's Chief Regulatory Officer.

The most mentioned external facilitators, advocates or champions in the signing and ratification of the AMA treaty are the Minister of Health, the AUDA-NEPAD, and Honourable Michel Sidibé, the African Union Special Envoy for the African Medicines Agency. According to respondents, the Minister of Health facilitated the process and supported NMRAs with communication and advocacy to government to ratify the treaty. The AUDA-NEPAD and the Special Envoy played an advocacy role, providing information about the AMA to NMRAs and governments, and Honourable Michel Sidibé also made courtesy visits to some AU member states to encourage the leadership to sign and ratify the treaty (P16). Other external facilitators include the RECs (namely the EAC and SADC), Permanent Secretaries for Health, the African Union and the African Union Commission, the WHO African Regional Office and WHO country offices, and the Ministry in charge of Foreign Affairs. Some external facilitators were mentioned only once by different participants and these were the Ministry in charge of East African Community Affairs, the Parliamentary Select Committee on Health, the Cabinet (P10), the PATH team (P10), the legal officer at the Ministry of Health (P10), AMREF (P10), and the pharmaceutical industry (P10).

4.3.7 Enabling factors for the signing of the treaty for the establishment of the African Medicines Agency

P7 considers *"the existence of NMRAs"* to be an important enabling factor for the signing of the AMA treaty. Building on this, one participant mentioned that for them, having a *"robust regulatory environment dating back to the 1960s"* (P22) is an enabler and another stated the *"presence of an organised system"* (P6) to be an enabler.

Another factor that participants consider to be important is the desire to have harmonised regulatory systems in Africa that allow for collaboration. For instance, it was stated by some respondents that *"the desire to establish an organisation that allows for regional harmonisation/international collaboration"* (P8) and the *"willingness for international cooperation and collaboration"* (P9) are enabling factors.

In addition, there must be strong political will and support from the parent Ministry and the government as well as appropriate advocacy to expedite treaty signing. Furthermore, the presence of internal facilitators, advocates, or champions in the NMRA enables treaty signing, especially when the advocates are the Heads of the NMRAs, and they have *"adequate awareness of the AMA treaty"* (P9). One participant (P16) also stated that the *"active participation of [their NMRA's] former Director-General in the AMA Steering Committee"* served as a facilitator of the treaty signing process. Moreover, there must be technical and financial resources for the process, and *"technical and financial support from external parties such as the AUDA-NEPAD, WHO and other donor organisations"* (P8).

According to P20, *"the creation of the African Continental Free Trade Area"* in their country served as an enabling factor for the signing of the AMA treaty.

4.3.8 The challenges or barriers encountered in signing the treaty for the establishment of the African Medicines Agency

Most of the participants from countries that have signed the treaty stated that there were no challenges or barriers encountered. The challenge mentioned the most is that the process is slow. Participants stated that there is a *"slow pace in processing the signing and ratifying the treaty"* (P3), *"the process is not moving and more advocacy from the AU needs to be done for the relevant stakeholders"* (P4), and there is *"administrative slowness"* (P18) and *"slowness of administration"* (P23). Participants also reported that there is a lack of awareness and limited understanding of the signing of the treaty. Additionally, in some countries *"the bureaucracy and red tape"* (P12) present a challenge and it is difficult to convince their leaders to sign. Competing national priorities, administrative and

legislative procedures, changes in office bearers in the public system and stagnation of the process at the ministerial level are also challenges encountered. One participant (P17) mentioned that they are *"keen to participate but there is little support in the processes that will follow".*

To overcome these challenges or barriers, NMRAs were *"pushing the concerned authorities to speed up the process"* (P3), calling for *"more political involvement"* (P19), and conducting *"more advocacy for the Ministers of Health, Foreign Affairs, Justice, and the Government"*. They also improved their follow-up of documentation at the Ministry of Health for the process to move along to the ratification stage. For example, one respondent stated that their solution to overcome the challenges is *"sensitisation of the Ministry of Health officials who are to push the process forward at the Cabinet and Parliamentary levels"* (P12). Dialogue and stakeholder engagement featured prominently as an advocacy strategy to create awareness among key stakeholders. Furthermore, some African NMRAs brought in *"strong external advocacy from international institutions (i.e., the AU, WHO, and SADC)"* (P18) and they are urging *"the AUDA-NEPAD, WHO Regional Office and WHO Country Office to advocate and help the NMRA to persuade the government to take quick response to sign and ratify the treaty"*. NMRAs also *"need the support of the AU to the Ministries and the Government".*

4.4 Part II - The agenda setting process leading to the ratification of the treaty for the establishment of the African Medicines Agency

In-depth semi-structured interviews were conducted with three key-informants from Ghana (n=2) and Rwanda (n=1). The description of participants is shown in Table 6 below. Two key-informants from Burkina Faso (n=1) and Mali (n=1) agreed to participate in the research study; however, a date and time for the interview could not be finalised. A senior official in the national medicines regulatory authority of Seychelles was also invited to participate in the research and they stated that Seychelles would not be a good case study to include in this research. This was due to the AMA treaty ratification having been done by the previous government and led by the past Minister of Health.

Table 9: Study participants

Key Informant	Participant description
KI1	Senior Management, Rwanda FDA
KI2	Senior Management, Ghana FDA
KI3	Senior Management, Ghana Ministry of Health
KI, key informant.	

The results of this section are presented according to the three streams of Kingdon's framework: the problem stream, policy stream, and politics stream.

4.4.1 The problem stream

The problem stream refers to the process of convincing policy decision makers to pay attention to one problem over another (89,91). Before something becomes defined by someone as a problem, it is simply a condition. The difference between a condition and a problem is that problems are considered to be something we ought to do something about (89). For a condition to become a problem, it often violates social norms, values and points of view. Conditions can also become problems when circumstances are compared with those observed or reported elsewhere (89,91,93).

There are several challenges faced by African countries when it comes to the regulation of medical products. For instance, "*Africa is managing most […] products produced outside the African continent"* and *"most of the African countries have weak regulatory systems"* (KI1). Additionally, a key informant stated that *"we had some issues when dealing with the Ebola vaccines and other pandemics, you know Ebola was near here – Congo"* (KI1). They further explained that *"there has been some Ebola vaccine trials so those also posed a challenge that you could be confronted to authorise a trial when really you don't have the competence to do so […] so, if this trial was to be conducted in African countries, in most of the African countries, countries would face a big challenge because I think few competent institutions can be able to authorise those trials"*

(KI1). *"The outbreak of Ebola and these other pandemics like COVID-19 was also some of the key factors that contributed to re-energise and put more speed in the establishment of the African Medicines Agency"* (KI1).

KI2 also highlighted that the lack of competent human resources is a challenge and a motivator for the establishment of the AMA. They stated that *"Ghana recognises the fact that collaborating and working together is always better than working individually because there is more strength in working in a collaborative effort and we have that example with EMA in Europe, and so that motivated us especially with the AMA treaty and establishing the AMA, I think issues to deal with the lack of expertise and others"* (KI2).

Furthermore, the circulation of substandard and falsified medical products poses a challenge to African regulators. It was reported that *"there are instances where you find that products are being counterfeited. But of course, I think we had seen as a country, we had seen that, you know, proper regulation of medical products is very critical and, though we have been trying to address the same issue, in Rwanda, we thought it would be very important also the issue to be addressed at a continental level […] Rwanda FDA we are always on top of that if we happen to identify or to get the info we always act as a regulator"* (KI1). Connected to the circulation of substandard and falsified medical products in Africa, KI3 highlighted that *"there are challenges of porous borders and movement of goods and services creates a situation where without a stringent regulatory mechanism you will miss out and not safeguard your people"* (KI3). KI3 also contends that *"in West Africa, for instance, I would say we have artificial borders; there is movement of goods and services across our country, and the only way we can be sure that what is entering Ghana is the same as what is leaving Ghana is to ensure that we are all operating in the same space. And that same space is what the African Medicines Agency seeks to provide"* (KI3).

Moreover, a continental institution to oversee the regulatory harmonisation and pharmaceutical manufacturing initiatives does not exist on the continent. Therefore, KI1 highlighted this as a problem that needs to be addressed: *"From the MRH programmes and the Pharmaceutical Manufacturing Plan for Africa,*

we [Africa] needed a body that will be able to regulate those initiatives that are coming up. If you are promoting the manufacturing on the continent, we need to have a very strong regulatory body to make sure that whatever is being produced are of acceptable quality standards" (KI1). There have also been challenges with timely access to medicines, therefore the AMA is seen as *"a very positive move in getting products to our populations on time"* (KI2).

4.4.2 The policy stream

The policy stream has the outputs of experts and analysts who examine problems and propose solutions (88). It is also in this stream where alternative solutions to a policy are generated (89,91,94). The numerous possibilities for policy action or inaction are identified, assessed, and narrowed down to a few feasible options (88). The policy proposals need to find a problem to become coupled to and also have considerable support in order to take priority on the agenda.

Considering the problems highlighted in the problem stream, African regulators and health leaders consider the establishment of the African Medicines Agency by treaty to be a viable solution to address the challenges faced on the continent. It is believed that *"having one strong regulatory system for the continent will be a plus"* (KI1) and it was reported that *"most of the countries have been eager to see how this specialised organ of the African Union can be established and contribute to the safety and efficacy of the products that we are consuming on the African continent"* (KI1). In addition, KI1, who had stated that *"there has been some Ebola vaccine trials so those also posed a challenge that could be confronted to authorise a trial when really you don't have competence to do so"*, highlighted that *"if we had AMA in place, that would have been able to critically analyse the trial, authorise the trial, and be able to stand in for Africa" […] So that's why I think having this specialised organ of the African Union that will look at the medical products regulation is very important"* (KI1). As a country, they also *"felt that we needed a strong regulatory body to at least push some of those regulatory approaches to make sure that we address such emerging pandemics and epidemics"* (KI1).

The AMA's establishment as a solution to reported problems in Africa is considered to hold promise to build capacity on the continent. The following narrative supports this point: *"So we understood the role of AMA as a continental agency, to play its role in guiding and strengthening regulatory capacities in different African countries, especially those that are very weak, that do not have legal instruments to regulate medical products, so we felt that, you know, that was also a motivating factor. And we felt that being, you know, having a continental body would also help us strengthen our regulatory agency - through capacity building, through collecting finance, finance mobilisation. So, we felt that that was very critical for Rwanda, and of course probably if it is hosted closer to Rwanda, or even in Rwanda, then we benefit more through the expertise sharing, resource sharing, experience sharing, so that was itself a motivating factor for us to move forward"* (KI1). KI2 also stated that capacity building is expected to result from the ratification of the AMA treaty and the establishment of the AMA:

> *"We think that it will give us the opportunity to get health products into the population earlier than we have been getting because I think these are part of the treaty. It will help us to build capacity in terms of health products and it will help our regulators to be able to solve some of the problems we have not been able to solve as at now. So, we think it is positive. It will help us to be more efficient, to rely on work done by assessors of international repute. It will help Africa to connect to Europe, the Americas, in terms of regulatory issues. We saw it as a very positive activity. A very positive initiative"* (KI2).

In addition, the AMA is expected to result in timely access to medical products in Africa. As KI2 indicated, *"relying on the collective results from evaluations and things will help us to get medical products on our markets in a very short time"* (KI2). KI2 also reported that *"because now we are all talking about reliance and so, if we have a body like the AMA, we can rely on the decisions that have been made in ensuring that our people get medical technologies in a quick time"* (KI2). From KI3's point of view, ratifying the treaty and establishing the

African Medicines Agency was also about creating harmonised medicines regulatory systems in Africa and risk sharing as highlighted below:

> *"Ghana is already at maturity level 3 of regulation and so we understand what it means if the rest of Africa agrees we harmonise our systems, and so that was what drove us and the fact that we felt it is the best thing to do for Africa, for ourselves, and for the generations after us. Of course, we also learnt of how the European Union had their harmonised systems and how it helped countries. Countries that otherwise would not have a good regulatory system are covered by those who have. So, the risk is shared. You have a risk shared among those who have very stringent regulatory authority and those who do not have, so that at the end of the day, they are not worse off. That they can have products that circulate in their market that is covered by at least what Africa considers to be the best option"* (KI3).

This key informant also stated that *"the establishment of the AMA as a continental regulatory body provides leadership to ensure that issues are harmonised and strengthened, systems are strengthened, and regulation is governed in terms of medical products and health technologies on the continent"* (KI3). Furthermore, KI3 recalled how when *"it was time for the AMA to be discussed [in Parliament]"*, they were called together with the Minister of Health *"to come and justify why we thought that A.M.A is important for Ghana"* (KI3) and they gave three reasons why it was important for the country to ratify the treaty. The first reason they gave was *"the fact that if we [Ghana] ratify the treaty, we had some benefits to derive from it, and those benefits include the fact that global trade requires us to be mindful of the fact that there are challenges of porous borders and movement of goods and services creates a situation where without a stringent regulatory mechanism you will miss out and not safeguard your people"* (KI3). Secondly, *"the ratification of the treaty supports the operationalisation of the Africa Continental Free Trade agreement […] of which Ghana hosts as a Secretariat. And then if we establish the AMA, it has associated benefits for the workings of the other agencies"* (KI3). The third justification to

ratify the treaty was that if Ghana does not ratify the treaty and *"allows the status quo to remain, it means that Ghana has changed its position in terms of the agreement that they have signed with the other African Heads of State, and that is not noble. It is not a noble thing to do if we agree with the, if our President agrees that it is the best thing to do and Ghana decides not to sign, that is not good enough. And so, we felt that the best thing to do is to ensure that this is done and done well. And so those are the things that we put forward and justify it and explain that the best thing to do is to make sure that the treaty is ratified, and Ghana can be counted among the Committee of Nations"* (KI3).

When asked if there were any perceived disadvantages of establishing the African Medicines Agency, all key informants stated that there were none. According to KI2, *"We did not think there would be any disadvantages. If we were thinking like that, I think we would not have ratified this, because I think normally sometimes the concern is whether that body is going to take over the work of a regulatory authority in-country but we, our understanding is that that is not the case. It will rather enhance the work of regulatory authorities in the individual member states of the African Union, so we did not have any reservations, but rather we saw it as a very positive move in getting products to our populations on time"* (KI2).

4.4.3 The politics stream

The politics stream refers to the political context and specifically the conditions that lead to receptivity of those with power to decide on policy solutions to address an identified problem.

For Ghana and Rwanda, the presence of political will and leadership, the desire to be pioneers in taking up continental initiatives, and actively participating in the development of the treaty for the establishment of the African Medicines Agency led to ratification of the treaty as a policy solution for Africa's medicines regulatory problems.

1. The presence of political will and leadership

In both Ghana and Rwanda, there was political will and leadership that strongly supported the ratification of the treaty for the establishment of the African Medicines Agency. According to KI1, *"Rwanda understood the need, I think even way before others because when you see the history, it tells us that Rwanda was the first country to sign the treaty, we also went ahead to be the first country to ratify the treaty, but also the first country to deposit the instruments in the African Union Commission. So, I think Rwanda felt this was an urgent need - to establish this Agency, and of course I think the importance we attach to this agency is clearly reflected"* (KI1). KI1 also stated that the country's top leadership was actively involved in the process of treaty signing and ratification, and they all understood the urgency of setting up a continental regulator. *"So, after the treaty had been endorsed by the African Union Heads of State, then it was pushed to countries to ratify – to make sure that the treaty is ratified, and then the institution can be established. So, for us when it was officially endorsed by the African Union, of course our task now was easy because our top leadership was on top of it, they understood the urgency. Of course, we had to move, the Ministry of Health was on top of it. So, we had to move with the rest of the processes"* (KI1). Political will and leadership also existed in Ghana to facilitate the AMA treaty's signing and ratification as alluded to by one participant from the country: *"Ghana believes in the tenets of the AU, and the fact that the African Medicines Agency idea, we think that is the best to happen to Africa, and secondly, we have a President who believes in the African Union actions and therefore it is important that we support and do all the technical things to ensure that in the Committee of Nations, the President is known for doing things as quickly as possible"* (KI3).

It was reported that there were no external advocates for Rwanda to sign and ratify the treaty. The country's top leadership and government entities were self-motivated to ratify the treaty as a policy solution. The following account illustrates this point: *"There was nobody who came in to advocate, to mobilise, to support – No. We had to take the treaty that was already endorsed, and we had*

to, you know, do our internal processes. So, the internal process is that the Ministry of Health had to write the drafts of the Presidential Order ratifying the treaty - the law ratifying the treaty which is approved by the Parliament - so we had to move them very quickly because we understood the urgency. So, it was even given a priority through the government channels; we pushed it through the government channels up to the Cabinet approval. So, when the Cabinet approved the draft law ratifying the Agency, it was very quickly, of course the Minister was pushing it, very quickly submitted to Parliament, and Parliament approved the treaty – the law ratifying the treaty. Of course, there was also a Presidential Order which was also approved in the same timeframe. So, after that then we had to publish in the official gazette and then we had to deposit the instruments of the ratification. That was the process. Nobody was ... we only understood the urgency of the Agency, and we understood the urgency of ratifying those legal instruments, and that was it. And I think it was a record time, I think we used around four months to finalise the process and deposit the instruments" (KI1).

In Rwanda, there were other activities, initiatives or agenda items that were being considered in the country at the time when discussions about the signing and ratification of the treaty were taking place. According to KI1, they *"were busy establishing the Rwanda Food and Drugs Authority which is currently operational, so it was also part of the agenda of the, for the Ministry of Health, but of course the AMA was given a priority because we wanted to make sure that we clear that and we submit the instruments, but also other key priority areas are being considered like you know the establishment and operationalisation of the Rwanda Food and Drug Authority, which we feel is a very key agency also to help regulate the pharmaceutical sector in Rwanda"* (KI1). At the Parliamentary level, there were also agenda items competing with the AMA treaty's discussion. However, the AMA treaty ratification and the AMA's establishment were very important and political will and leadership existed to ensure that they are made a priority at different governmental levels. KI1 emphasised this point as they indicated that *"there are always competing priorities, but I think it also depends on how you prioritise the item. Because I remember when we submitted the law to the Parliament for consideration, the Prime Minister wrote a letter*

highlighting the urgency, so he was requesting them to make it a priority. So, I think that was also made it possible to move fast because it was given that priority that it was requested for. So, there might be other agenda items that are a priority, but I think priorities are also ranked and you should be able to prioritise according to the urgency of the activity" (KI1).

2. The desire to be pioneers in taking up continental initiatives

Both Ghana and Rwanda have pan-African leaders that take pride in their nation's identity as well as being an example for other countries to emulate. This is evidenced by KI1's response to a question that asked what the enabling factors and facilitators were that led to the signing and ratification of the AMA treaty: *"I think it's the commitment and the government's will to push. First of all, the understanding of the urgency of the treaty, being to establish the AMA, and of course, Rwanda being part of the AU, being in most cases the champion of the, most of the everything, we wanted to at least show that, you know, Rwanda is ready to be exemplary to move this, the signing and ratifying of the treaty. There was nothing behind it, so it was just, you know, trying to meet its obligation as an African member state"* (KI1). KI1 also stated that their *"leadership is very committed to moving forward especially the continental priorities"* (KI1) and therefore Rwanda *"was the first country to sign, was the first country to ratify, was the country first to deposit the legal instruments to the African Union Commission. So, and I think also that also motivated us, you know, we wanted to be always probably to be the first country to comply with some of the continental obligations"* (KI1). *"Rwanda is always happy to participate in African initiatives"* (KI1).

Expressing the same view, a participant from Ghana also highlighted that their *"President is very methodical regarding some of these obligations in the African Union and so having appended his signature to make sure that we have the African Medicines Agency treaty then it just enables us, because it is the same President who agreed with his fellow Presidents that this has to be done. And so, you cannot go back on your word and say do not ratify it. Because it is one of the … the ratification is one of the key actions that must follow. Of course, you just*

need fifteen countries, but he made sure that Ghana remains one of those fifteen that ratifies it before it becomes a treaty [in force]" (KI3). KI3 also stated that *"Ghana dominates a wider appeal to both national and international stakeholders and beneficiaries that since we are already at maturity level 3, we are showing the way, we are telling other African countries that look, it is not about Ghana alone, it is about all of us and so together we move, divided we will fall"* (KI3). Furthermore, the participant believes that *"in the Committee of Nations, it is important that we [Ghana] rise to the challenge of making sure that we ratify the treaty. And remember, Ghana is the star of Africa – the Black Star of Africa […] and we choose to lead"* (KI3).

3. Active participation in the development of the AMA treaty

For Ghana and Rwanda, the process to sign and ratify the AMA treaty did not start when the treaty had been endorsed by African Ministers responsible for Health. It began with active participation in the development of the AMA treaty as reported by KI1: *"You know, when we started the treaty development, Rwanda was part of the countries that never missed any meeting or any workshop that was developing the treaty. So, we participated in every meeting because we had understood the need and urgency of the treaty"* (KI1). The key informant from Ghana supported this point as they reported that staff from their national medicines regulatory authority were members of a Technical Working Group that developed the AMA treaty, *"and they work so hard to ensure that the tenets of the AMA reflect countries' aspirations for Africa"* (KI3). KI3 also expressed a view that the Ghana FDA *"was a very important agency in the harmonisation process in terms of how the articles are put together and how they reflect the aspirations of Africa"* (KI3). In addition, KI3 highlighted that due to Ghana's technical regulatory personnel from the FDA being part of the TWG, they (at the Ministry of Health) would *"get regular updates as to what was going on"*. Therefore, once the treaty had been endorsed and ready for countries to sign and ratify it, there was no hesitation in Ghana to do so. *"It was just so obvious, a natural choice that we consider that it is important Ghana does this, and Ghana … because Ghana supported it from day 1, first as members of the Technical*

Working Group, and then secondly as a government who believes that Africa united as one is the way to go if we want to open up our markets for value for managements" (KI3). This early involvement in the development of the AMA treaty and governance structure of the proposed continental regulator played a crucial role in the politics stream as well as in the agenda setting process leading to the ratification of the treaty in both AU Member States. Moreover, there were no perceived disadvantages to the establishment of the AMA in both countries. KI3 mentioned that they *"did not perceive any disadvantages at all […] we believe in harmonisation of regulatory actions in the continent. It is in Ghana's interests that the, all the agencies are harmonised in such a way that we get value for money"* (KI3).

4.4.4 Coupling of the streams: policy entrepreneurs and policy windows

According to Kingdon's multiple streams framework, there must be a coupling of the problems, policy, and politics streams for issues to appear on the agenda. This is done through the active participation of "policy entrepreneurs" who take advantage of policy windows and focusing events.

For the African Medicines Agency treaty to make it onto the governmental agenda, there were policy entrepreneurs in both Ghana and Rwanda. In the former, KI2 reported that the Head of the Ghana FDA and the Director for Technical Coordination in the Ministry of Health were policy entrepreneurs for the AMA treaty signing and ratification process: *"I think my Chief Executive Officer, Mrs. Delese Darko was somebody who was, who facilitated the signing by making sure that for every information that we hear from AUDA-NEPAD with regard to the treaty is passed on to the Ministry, and in the Ministry of Health, there is a Director for Technical Coordination, in the person of Dr. (Mrs.) Gyansa-Lutterodt was also, played a significant role. At least I remember these two. I think they played a significant role in making sure that it was not just something that we were wishing for but our wishes were translated to actions that has resulted in us ratifying the treaty"* (KI2). In Rwanda, KI1, a senior member of staff at the Rwanda FDA, was a policy entrepreneur and they attended several meetings during the AMA treaty development phase. KI1 stated that they

attended *"most of the meeting, I think the first one I attended, you know … by then the Rwanda FDA was still in the development stage, was trying to establish the agency, so I was being the person who was in charge of these medical product regulation under the Ministry of Health. I had to attend most of the meetings. We attend a meeting in Johannesburg, uh, Midrand. We attend a meeting in Tunisia, we attend a meeting in Ethiopia, and we attend a meeting, uh, maybe in Zimbabwe if I remember very well. So, there were around four five minutes, meetings, which were dealing with this. Also, I had to attend some of the meetings that were presented in the African Union meetings when the STCs were being convened. So, AMA was also part of the agenda to be discussed. So, series of meetings. I attended most of the meetings"* (KI1). KI1 also stated Rwanda's Ambassador in Ethiopia was a policy entrepreneur: *"You know, I think the most powerful, the most person who were behind this I think was by then the Ambassador, our ambassador in Ethiopia, and the Ministry of Health of course and under the where we were working and of course who was pushing all of the other government institutions to make sure that this treaty is being given the right priority it deserves. That is how I would mention it"* (KI1). The Ambassador played an advocacy role and they were *"pushing home office, was pushing us in the country to speed up the process because she was, she is at the AU Headquarter so she understands that the treaty has been, in fact she is the one who signed on behalf of the government, so she knows how urgent, of course we knew the urgency but also she was pushing us to make sure that we ratify the treaty as soon as possible so, we worked together with her, with the Minister of Health, to push all the legal instruments to make sure that the treaty is ratified"* (KI1). It is worth noting that KI1 reported that in their country, the agenda setting process for the AMA treaty's signing and ratification was not the result of one person's work – there were several policy entrepreneurs in different government offices. In Rwanda, *"the entire government from the top, His Excellency, was on, you know, were very passionate about the agency, was very passionate about pushing everything, so everybody in Rwanda you know, if something is given priority, we all take it on our shoulders. So, it was not one person's, uh, initiative"* (KI1).

In terms of policy windows, KI3 reported that the AMA treaty was signed by Ghana in Cairo, Egypt where a meeting was being held by *"the Social Admin bloc and the environment was just appropriate for it to be signed because the, Her Excellency was there herself and all the officers of the AU were in Cairo, and I think it was just appropriate and we seized the moment to sign the treaty"* (KI3). Additionally, Ghana had *"just received the nod to host the African trade secretariat. And so, it is just appropriate that we do the needful. And so, I think that those are the things that engineered the processes to ensure that we ratify it"* (KI3). For Rwanda, the window of opportunity to sign and ratify the treaty opened partly due to the President being the Chair of the African Union when the treaty was being endorsed. The President is said to have *"been pushing [for] the African Continental Free Trade, he is the Chair of the NEPAD, so he is pushing so many initiatives on the continent. So, we wanted to play our role as one of the member states too"* (KI1).

4.5 Summary

This chapter presented the findings of this research study in three parts. Part I was on the domestication and implementation of the African Union Model Law on Medical Products, Part II dealt with the signing and ratification of the treaty for the establishment of the African Medicines Agency, and Part III was on the agenda setting process leading to the ratification of the treaty for the establishment of the African Medicines Agency. The next chapter will discuss the findings of this study.

CHAPTER FIVE

DISCUSSION

5.1 Introduction

This chapter will discuss the results of this study. The study sought to analyse in-depth the rationale, perceived benefits, enabling factors and challenges of domesticating and implementing the AU Model Law on Medical Products Regulation by AU Member States and of the establishment of the African Medicines Agency. The results of this study will be discussed in three parts and key findings will be discussed in comparison to the literature. This chapter will focus on the domestication and implementation of the AU Model Law on Medical Products Regulation, the signing and ratification of the treaty for the establishment of the African Medicines Agency, and the agenda setting process leading to the ratification of the AMA treaty.

5.2 The domestication and implementation of the AU Model Law on Medical Products Regulation

The main purpose of medicines regulation is public health protection as well as to ensure that medical products circulating on national markets and in international commerce are quality-assured, safe and efficacious, and that they are used in accordance with good practices (111). As an important aspect of public health, medicines must be available and accessible to the public (111). It is also crucial that good governance exists in the pharmaceutical sector to improve access to medicines. Good governance refers to the formulation and implementation of appropriate policies and procedures that ensure effective, efficient and ethical management of medicines regulation in a transparent and accountable manner (111).

All the countries in this study have an NMRA or an administrative unit that is responsible for the regulation of medical products and nearly all the NMRAs that participated in this survey stated that there is legislation in place for medicines regulation. In some countries, legislation for medicines regulation dates back as far as 1957 whereas in other countries, legislation first came into effect as recently

as 2020. Most countries have also updated their legislation at least once and some are currently doing so. These findings are consistent with those reported by Ndomondo-Sigonda and colleagues (9). Additionally, this study found that countries update their legislation for medicines regulation for reasons such as the desire to establish a new regulatory authority, to transform the existing regulatory authority, or to align their legislation with the AU Model Law and international best practices. It is worth noting that a third of the NMRAs that participated in this study reported that they have domesticated the model law and over 90% are yet to do so despite the AMRH initiative, within the framework of the AU Pharmaceutical Manufacturing Plan for Africa, having set a target in its AMRH Strategic Framework (2016-2020) to domesticate the AU Model Law in at least 25 AU Member States by 2020. This target has not been achieved. Our study found that in order to achieve this target, there must be support for regulatory harmonisation and international collaboration in AU Member States as well as the availability of resources, the presence of political will and leadership, the desire to have an efficient and effective regulatory system, and the presence of facilitators/champions for the cause.

According to literature, the pharmaceutical sector is incredibly dynamic, characterised by several distinct stakeholders with diverse interests, and this creates a scenario where pharmaceutical policy cannot have a "one size fits all" approach (24). The process of policy development is almost exclusively a national matter and will differ among countries and regions with disparate levels of income (112). Countries and RECs with similar objectives may need different policies, taking into consideration their respective starting positions, pre-existing laws and regulations, and implementation capacity (24). Therefore, it is not surprising that in our study countries had different processes of AU Model Law domestication and they either domesticated the model law in full or they are conducting a partial domestication.

In terms of the domestication process, this study found that the process typically involves the NMRA's legal unit and the legal committee reviewing the existing legislation against the AU Model Law. Afterwards, the NMRA's legal unit and

legal experts develop a draft law which is then reviewed by the Legal Committee. The draft law is then circulated to stakeholders for comments and final revisions are made by the NMRA's legal unit to incorporate any comments. The Legal Committee has the responsibility to approve the final draft law and it is then submitted to the Minister of Health for approval. Next, the draft law goes to the Attorney General's office for approval, and then to Cabinet, and finally to Parliament. If Parliament approves of the draft law, it is then published in the government gazette. This process involves a number of stakeholders and multiple steps, resulting in it being lengthy and highly bureaucratic. It therefore needs facilitators, champions or advocates for the domestication and implementation to occur and these can either be internal, that is within the NMRA, or external. The internal facilitators identified in this study are lawyers working in the NMRA's legal unit/department, technical staff, the Head of the NMRA, and the focal person for the regional medicines regulatory harmonisation initiative. The external facilitators include the Ministry of Health, the AUDA-NEPAD, the WHO African Regional Office, the regional economic community, the World Bank, and the WHO country office. One country reported the local pharmaceutical industry, non-governmental organisations and academia to be key external facilitators in this process. It is important to have all stakeholders involved early in the process as it will result in a stable system that can guarantee access to and rational use of medicines (112). Additionally, African countries with the greatest disease burden also have the most resource limited NMRAs (113). NMRA regulators in 26 African countries were interviewed by WHO assessment teams which found that across the board, there exist weak management structures and processes, a severe lack of qualified personnel, and scarce resources (113). Therefore, it is at this early stage when all stakeholders are involved that national priorities need to be defined based on a balance between meeting the needs of patients and ensuring the effective use of available resources (112).

Policy implementation is a major problem in low-income countries (114). Failures in achieving the desired policy goals can be attributed to inadequate resources, a lack of communication bridging research to policy, an absence of a

strategy, governance instability and a lack of political commitment (114). In our study, the challenges or barriers encountered in the process of domesticating and implementing the AU model law include the lack of human and financial resources, competing priorities at the national level, overlapping roles of government institutions, and the process of amending/repealing laws being slow and lengthy. Hoebert *et al.* (112) report similar challenges in pharmaceutical policy implementation and contend that the process requires sufficient staff with appropriate technical and professional capabilities (112). They also found that some policies that affect medicines contradict or undermine others (112). However, they do admit that the process of deciding which functions fall into which area is a complex one, and the decision to proceed as well as the subsequent success of implementation is dependent on political support and capacity at the local level (112). Furthermore, shortcomings in regulatory performance, lack of access to medical products and irrational use of medicines may exist despite the existence of a comprehensive policy document (112) In our study, one of the ways that participants addressed the challenges that they encountered in AU Model Law domestication and implementation was to approach their governments and various stakeholders and lobby them to adopt the model law, and they had frequent communication, consultations, and discussions on the importance of domestication of the model law. In addition, NMRAs requested assistance from development partners such as the World Bank, through the AUDA-NEPAD, the African Union, WHO, RECs and other international bodies. These partners have prior involvement in the regulatory landscape in Africa, particularly in the AMRH initiative. Literature confirms that the involvement of external stakeholders and garnering high-level political support enables the development and implementation of a policy. For instance, when South Africa was developing its first single National Medicines Policy, it invited the WHO to participate from the start and this high-level political support resulted in the final policy document in 1996 (112). The support also ensured the successful implementation of most of the national components of the policy in the years that followed (112). Furthermore, our study found that in countries where the AU model law's domestication was challenging due to overlaps in roles, duties, and

responsibilities of the NMRA and another government institution, a solution that was being considered was the demarcation of roles, duties and responsibilities. NMRAs also sought funds to support the process and in cases where the process was slow and lengthy, timelines were extended to allow industry and stakeholders time to provide input.

In this study, the perceived benefits of domesticating and implementing the model law are to enable cooperation with other NMRAs, to harmonise regulatory systems and to facilitate mutual recognition between and amongst countries. This finding can be explained by Ahonkhai and colleagues' analysis (113) which found several complexities in the current regulatory system such as disparate NMRA standards and requirements in low- and middle-income countries (LMICs). This leads to additional work and duplicative efforts for manufacturers when submitting marketing authorisation applications in different African countries (113). Taking into consideration the limited commercial returns in LMICs, eliminating duplicative efforts and adopting a common set of technical product registration requirements makes sense (113). The finances and time needed to write, re-write and manage applications from one country to another remains a disincentive for manufacturers (113). In Europe, concerns about greater consistency and optimised access to quality-assured medicines was one of the strongest motivators for developing a unified pharmaceutical regulation approach that exists today in the European Union. Other common perceived benefits of domesticating the model law that emerged from our research include being in line with regional international standards and best practices, facilitating the exchange of regulatory information, improving the regulation of medical products, curbing the circulation of substandard, falsified and illicit medical products, and having an NMRA that is fully mandated to carry out regulatory activities. Additionally, it is perceived by NMRAs that model law domestication will result in an increased number of registered medical products. According to literature, pharmaceutical manufacturers tend to spread submission of new products to African NMRAs over several years and Ahonkhai *et al*. (113) identified a number of potential root causes of this situation. These root causes include the fact that multi-national companies did not typically prioritise early registration and

introduction of innovative medical products into low-income countries due to limited commercial potential in these markets. Secondly, low-income countries have varying requirements and legislative frameworks that limit manufacturers' ability to submit a single dossier concurrently to these countries (113). The spread is further exacerbated by the enormous resources required to prepare unique submissions for each country as well as respond to the queries from each individual NMRA (113). Therefore, some countries experience long waits before they receive marketing authorisation applications (113). It is evident that NMRAs hope that the model law will address the status quo.

An interesting perception stated by a participant in our study was that domesticating and implementing the model law would enable the regulated community to clearly understand their roles. This is important as we note that in Sri Lanka, the first two attempts (in 1991 and 1996) to develop a National Medicines Policy failed due to strong lobbying against it by the private pharmaceutical industry even though they had participated as a stakeholder (112). This demonstrates how it is important to get buy in from the pharmaceutical industry and have them clearly understand the importance of pharmaceutical policies and their roles. In addition, the model law's domestication and implementation was perceived to result in a strong, autonomous regulatory authority, improve transparency and efficiency of the medicines regulatory framework and safety monitoring systems, and enable countries to have appropriate laws that include all regulatory functions expected of a national medicines regulatory authority. This ensures that medicines distributed in countries are safe, efficacious and of good quality. Furthermore, the domestication and implementation of the model law is perceived to result in better oversight of clinical trials, increase export opportunities for domestic pharmaceutical manufacturers, increase confidence in the health system and medicines, and reduce antimicrobial resistance. Moreover, being the first country in the region to adopt and domesticate the AU model law was considered beneficial as it would bring attention to the country's NMRA and enable it to participate in regional and continental harmonisation initiatives. It was also interesting to see a participant in our study making the link between AU model

law domestication and enabling them to participate in the realisation of the AMA project. This is in line with literature that states that the long term goal of the AMRH initiative is to establish the African Medicines Agency, which will have the mandate of overseeing the registration of specific medical products and coordinating regional harmonisation systems in Africa (14,23). Therefore, the development of the AU Model Law is interpreted within the context of these overarching efforts towards regulatory harmonisation in Africa (14). These efforts in regulatory systems harmonisation are a pivotal aspect when laying the foundation for establishing a single African Medicines Agency (3,13,14,23,47,58).

In this study, most respondents stated that there were no perceived disadvantages of domesticating the model law. However, those that did considered the lengthy process of amending existing Acts to be a disadvantage. According to literature, law amendments are a lengthy process that requires two vital steps: (i) ensuring precise technical wording of the policy, and that it is consistent with other national laws and can be implemented; and (ii) passing the policy amendments through the formal, established, legally required administrative processes (21). In principle, solutions to address the challenges related to pharmaceutical policy and regulatory reform are relatively straightforward; however, the implementation aspect of the process is very much complicated (19).

Another perceived disadvantage of domesticating the model law stated in this study is that the expanded mandate brought about by the AU Model Law may not be affordable. As it stands, many LMICs cannot finance their public health needs and their NMRAs are particularly vulnerable (25). African NMRAs have relatively small annual budgets and a significant amount of the budget is earmarked for operational costs. This leaves a relatively small amount for salaries and infrastructure development (115). According to studies conducted by Ndomondo-Sigonda *et al.* (115) in the EAC region and Sithole *et al.* (116) in the SADC region, African NMRAs use different financing models. Generally, they obtain funds from their governments, fees for services provided (i.e. fees for registration, annual product maintenance, plant audits, licensing of premises, and

import permits) and/or from donors (9,25,115,116). In some African countries where the NMRAs depend on government funding, all fees are paid directly to Treasury. These fees are not redistributed and the funds allocated by the respective governments to their NMRAs are not released in a timely manner (115). While most African NMRAs levy fees, they tend to charge arbitrary amounts that are not commensurate to their regulatory workload or value-added activities (25). This creates a market entry barrier, hinders post-marketing quality surveillance, and prevents potential financial sustainability (25). Based on these factors, NMRAs cannot pay competitive salaries or sustainably finance workforce capacity development activities. Fortunately, African countries can domesticate the AU Model Law on Medical Products Regulation which is a non-prescriptive model legislation that assists them to amend, repeal and/or enact laws that grant NMRAs the power to levy, collect and use fees for services that they render (25).. Lastly, in this study, all participants who stated that they have implemented the AU Model Law reported that there have been no disadvantages to its implementation. It is important that mechanisms for implementation and monitoring are created after the official adoption of a policy (112).

5.3 The signing and ratification of the treaty for the establishment of the African Medicines Agency

Supranationalism is a politico-legal concept that denotes the existence of a multi-level governance system with regional institutions exercising authoritative powers over member states (117). Supranationalism has decisional autonomy and the binding effect of organisation laws as its core elements (118,119). The objectives of the integration process are either expressly stated in a constitutive treaty or implied by the nature of powers conferred on the organisation by its member states. This part of the research study focused on the signing and ratification of the AMA treaty which serves to create a supranational regulatory authority. A number of attempts at supranationalism have been made in Africa over the years and some of these attempts have succeeded while others have failed (120). The ones that have made significant progress are for monetary, business, security and judicial affairs (120).

The AMA is believed to have the unique opportunity to become one of the most efficient and modern regulatory systems in the world (121). This opportunity can quickly become reality by using the experience acquired over the last ten years of harmonisation activities in Africa, lessons learned during the COVID-19 pandemic as well as the expedited implementation of modern and innovative solutions (121). Drawing lessons from previous supranationalism successes, African states participate in regional integration initiatives due to the desire to accrue immediate to long-term benefits and if a country loses out on the benefits, it is likely that the country will either partially commit to the objectives of integration or completely pull out (120). In our study, the perceived benefits of establishing the AMA are that the continental agency will enable reliance and recognition mechanisms to be implemented by African NMRAs, enable access to medical products across the continent, improve regulatory systems across Africa, develop NMRAs' regulatory capacity and expertise, as well as to enable regulatory harmonisation on the continent.

According to literature, a number of factors may influence ratification and these include elements such as the substantive content of the treaty, its relative legal strength, and the current political regime in the ratifying country (122). In our study, the enabling factors for the signing of the AMA treaty were the existence of NMRAs. All countries in Africa (with the exception of Sahrawi Republic) have an NMRA or an administrative unit conducting some or all expected NMRA functions (9). However, there is wide divergence of regulatory oversight in Africa with some countries having robust and functional NMRAs whereas other countries have virtually non-existent regulatory systems (7–9,13–15,53). There are also varying corporate profiles of NMRAs in Africa as some are lawfully established as body corporate whereas others operate as departments or units under their respective Ministry of Health (9,26,36,48). The NMRAs in Africa have variable functionalities and they are at different growth, expertise and maturity levels (9). Despite the differences between NMRAs in Africa, the existence of a regulatory body serves as an enabling factor as well as the desire to have harmonised regulatory systems in Africa that allow for collaboration. As it stands, five out of the eight RECs in Africa (the EAC, ECCAS, ECOWAS,

IGAD and SADC) have medicines regulatory harmonisation initiatives, although at different maturity levels. In addition, there has to be strong political will and support from the parent Ministry and the government as well as appropriate advocacy to expedite treaty signing. Furthermore, the presence of internal facilitators, advocates or champions in the NMRA enables treaty signing, especially when the advocates are the Heads of the NMRAs and they have adequate awareness of the AMA treaty. Moreover, there has to be technical and financial resources for the process, and technical and financial support from external parties.

The majority of participants in our study stated that their NMRAs/countries did not have any perceived disadvantages to the establishment of the AMA. However, those that did voiced that if the AMA is operationalised, some duplication of effort may be present. Duplication of effort is a possibility due to some countries, e.g. Tanzania, being a member of two RECs – the EAC and SADC – where their NMRA actively participates in regulatory work. Therefore, once the AMA is established, TMDA staff may find themselves in a situation whereby they do work for the national regulator, two regional medicines regulatory harmonisation initiatives, and for a continental regulatory authority. Literature supports this finding and scholars contend that having multiple RECs with overlapping and replicated membership has contributed to failures to integrate and establish supranational institutions (120). This is due to the RECs lacking unity in their approaches and goals. Out of 54 African countries outlined in their book chapter (120), only 5 are members of one REC, 27 belong to two, 17 belong to three, and 3 belong to four RECs.

Participants in our study also felt that the scope and mandate of the AMA is ambiguous and there are fears of the AMA taking up the roles of NMRAs. The AMA was expected to be launched in 2018 (31,36), and the treaty establishing it entered into force three years later on 5 November 2021 when the 15th instrument of ratification was received by the African Union Commission (123). The perceived disadvantages stated in our study may be the reason why the AMA treaty ratification process has been slower than anticipated by its proponents and

also why some countries with better regulatory systems are yet to ratify. In Africa, there is typically a considerable difference between commitment to supranationalism at public fora and the creation of an environment that is conducive for operational success (120). This is attributed to lack of political will on the part of African governments to bring goals and objectives to fruition (124). Lack of political will has in the past hindered attempts at supranationalism on the continent regardless of whether monist or dualist legal frameworks are used (125).

Other perceived disadvantages to the AMA's establishment raised in our study are that once the AMA is established and their country signs and ratifies, there will be a requirement for eventual financial contribution on the already overstretched country budget. Many LMICs cannot finance their public health needs and their NMRAs are particularly vulnerable (25). Currently, the African governments are already failing to meet health financing targets. In April 2001, AU Member States met in Abuja, Nigeria where they committed to allocate 15% of their government budgets to health (126). This commitment is referred to as the 'Abuja Declaration' and in any given year, only a handful of African countries have met this target. For instance, only two countries met the target in 2018 (126). Due to underperforming economies which result in some AU Member States being unable to meet their financial obligations to the sub-regional organisations that they belong to, the establishment of supranational organisations has been unsuccessful (120). The AMA will therefore require sustainable financing mechanisms to enable it to operate successfully.

Furthermore, our study participants raised concerns about whether countries with very limited regulatory capacity will have a voice or will have their needs catered for within the institution. The fear of our study participants is that the AMA once operational may cater more for those with greater regulatory capacity. This is valid as regional integration has often resulted in African countries with stronger economies accruing maximum benefit from the integration initiatives to the detriment of other member states (120). For instance, Kenya benefitted the most in the old EAC due to it being a relatively developed country. Several measures

then had to be put in place to rectify the imbalances and these included the adoption of a transfer tax system. One of the aims of this system was to ensure Tanzania and Uganda's industries operate efficiently through the provision of additional budgetary revenues (127). Moreover, there is a fear stated by our study participants that once the AMA is operational, those with lower (WHO) maturity level will continue to be left behind. This fear hinders establishment of supranational institutions as it causes smaller AU member states to opt not to support regional organisations that are believed to be *"the mouthpiece"* of regional powers (120). These regional organisations then lose legitimacy (120).

In our study, the challenge related to treaty signing mentioned the most is that the process is slow. We found that there is a slow pace in processing the signing and ratification of the treaty and in some cases, there is a lack of awareness and limited understanding of the signing of the treaty. Additionally, we found that there is bureaucracy and red tape in some countries which presents a challenge and it is also difficult to convince the leaders to sign. Competing national priorities, administrative and legislative procedures, changes in office bearers in the public system and stagnation of the process at the ministerial level are other challenges encountered. Scholars of supranationalism report that regional institutions in Africa are expected to function based on *"the whims of member states […] rather than to fulfil the ambitious objectives of the organisation".* As a result, there are examples in literature of integration initiatives being derailed or dissolved following changes in administration in member states or due to personal difference among Heads of States and Governments (120). The lack of independence of regional institutions therefore impedes the implementation of integration initiatives (120).

The treaty signing and ratification process therefore needs facilitators, advocates or champions to address some of these issues, and they can either be internal, that is within the NMRA, or external. In our study, the Head of the NMRA was the most cited internal facilitator along with the NMRA's Board. Their roles involved advocacy at the ministerial level, spearheading the signing and ratification of the treaty, as well as preparation of the Bill and explanatory memorandum/concept

notes. Other internal facilitators mentioned in our study include NMRA staff, including the legal departments and committees, pharmacists, the NMRA's focal person for the regional medicines regulatory harmonisation initiative, and the NMRA's Chief Regulatory Officer.

In terms of external facilitators, advocates or champions in the signing and ratification of the AMA treaty, the people or entities most mentioned were the Minister of Health, the AUDA-NEPAD, and Honourable Michel Sidibé, the African Union Special Envoy for the African Medicines Agency. Honourable Michel Sidibé was appointed on 26 March 2021 by the AU Chairperson, H.E. Moussa Faki Mahamat, to carry out high-level advocacy activities on the AMA treaty ratification and this involved leading advocacy missions together with the Commission to AU Member States that have signed but not yet ratified the AMA Treaty, in order to expedite the AMA treaty coming into force (128).

5.4 The agenda setting process leading to the ratification of the treaty for the establishment of the African Medicines Agency

The explanation offered by Kingdon on how agenda setting works focuses on three streams: problem, policy, and politics (88,89,92). Before something becomes defined by someone as a problem, it is simply a condition. The difference between a condition and a problem is that problems are considered to be something we ought to do something about (89). For a condition to become a problem, it often violates social norms, values and points of view. Conditions can also become problems when circumstances are compared with those observed or reported elsewhere (89,91,93). In the problem stream of our study, several challenges faced by African countries related to the regulation of medical products were reported by participants. These include the fact that the majority of medical products that are regulated by African NMRAs are manufactured outside the continent and most African countries have weak regulatory systems. There are also challenges faced with authorising clinical trials and reviewing marketing authorisation applications for complex products such as vaccines. Additionally, there are human resource constraints in NMRAs and substandard and falsified medical products circulate in some territories partly due to porous

borders. Moreover, the lack of a continental institution to oversee regulatory harmonisation and pharmaceutical manufacturing initiatives is considered to be a problem that needs addressing. Countries are therefore cognisant of the importance of robust regulatory systems. All these conditions became defined by policy entrepreneurs as problems as they were considered to be something that ought to be rectified, and they violated social norms, values and points of view. When Africa's lack of a continental regulator was compared with the existence of the Europe's European Medicines Agency and how it functions, the conditions also became problems.

In our study, African regulators and health leaders consider the establishment of the African Medicines Agency by treaty to be a viable solution to address the challenges faced on the continent. It is believed that one strong continental regulator is good for Africa and most countries are keen to see how the specialised organ of the African Union can be established and contribute to ensuring the quality, safety and efficacy of medical products consumed on the continent. The AMA is also expected to result in clinical trial applications being critically analysed and authorised in Africa as well as address emerging pandemics and epidemics.

In addition, the AMA's establishment as a solution to reported problems in Africa is considered to hold promise to build regulatory capacity on the continent, especially that of NMRAs that are weak and do not have legal instruments to regulate medical products. The enhanced regulatory capacity is expected to, *inter alia*, improve access to medical products on the continent. One of the ways that medical products can get faster marketing authorisation in Africa is through instituting reliance mechanisms. Another motivating factor for ratifying the treaty and establishing the African Medicines Agency was the desire to create harmonised medicines regulatory systems in Africa and sharing risk. This point came from a participant from one of the few African countries that have attained WHO maturity level 3 status. Furthermore, our study found that one of the justifications in Parliament to ratify the AMA treaty was the fact that countries considered it beneficial for them to do so for various reasons. Another

justification to ratify is that it is the noble thing to do. In our study, no perceived disadvantages of establishing the AMA emerged.

In Kingdon's framework, the politics stream refers to the political context and specifically the conditions that lead to receptivity of those with power to decide on policy solutions to address an identified problem. Our study found that for Ghana and Rwanda, the presence of political will and leadership, the desire to be pioneers in taking up continental initiatives, and actively participating in the development of the treaty for the establishment of the African Medicines Agency led to ratification of the treaty as a policy solution for Africa's medicines regulatory problems. In terms of the presence of political will and leadership, our study found that in both countries, there was strong support for the ratification of the treaty for the establishment of the African Medicines Agency and the countries' top leadership was actively involved in the treaty signing and ratification process. They also all understood the urgency of setting up a continental regulator. It was reported that there were no external advocates for the two countries to sign and ratify the treaty. The countries' top leadership and government entities were self-motivated to ratify the treaty as a policy solution. In Rwanda, there were other activities, initiatives or agenda items that were being considered in the country at the time when discussions about the signing and ratification of the treaty were taking place. At the Parliamentary level, there were also agenda items competing with the AMA treaty's discussion. However, the AMA treaty ratification and the AMA's establishment were very important and political will and leadership existed to ensure that they are made a priority at different governmental levels.

Both Ghana and Rwanda have pan-African leaders that take pride in their nation's identity as well as being an example for other countries to emulate. These countries both believe in supporting AU initiatives and are motivated by the desire to be the first, or one of the first, countries to act. Our study found also that for Ghana and Rwanda, the process to sign and ratify the AMA treaty did not start when the treaty had been endorsed by African Ministers responsible for Health. It began with active participation in the development of the AMA treaty. This

early involvement in the development of the AMA treaty and governance structure of the proposed continental regulator played a crucial role in the politics stream as well as in the agenda setting process leading to the ratification of the treaty in both AU member states. Moreover, there were no perceived disadvantages to the establishment of the AMA in both countries.

The three streams in Kingdon's framework are generally independent, flowing along different channels, governed by their own rules and processes which have an impact on the movement of events on the agenda (88,91). These three streams do not necessarily follow each other in a sequential or logical order (91). However, at specific critical points in time, these separate streams cross and a 'policy window' opens (88,89,91,94). Problems are then coupled to solutions, and both are joined to favourable political forces resulting in an issue getting recognition as a problem on the official or institutional agenda, and the public policy process then begins to address it (88–90). Policy change can only occur when all three streams come together and if the streams do not cross, the policy change will either not occur or be considerably difficult to obtain (90,92,94). The coupling of problems to solutions, and both of these to political opportunities is done by 'policy entrepreneurs'. Policy entrepreneurs are people who invest their resources in advocating for their pet proposals or problems, and prompt important people to pay attention. They have a critical role to play in shaping the course of the three streams and with tenacity, knowledge and power, they attempt to further their own policy aims in government's agenda in order to solve specific problems (88,89,94). The opening of policy windows, which occurs quite infrequently, can be triggered by seemingly unrelated external focusing events such as crises, accidents or the presence (or lack thereof) of policy entrepreneurs both within and outside of governments (88,89). The policy windows can also be opened by institutionalised events such as elections or deadlines (88,89).

Our study findings are in agreement with the points raised in the previous paragraph as we observed that for the AMA treaty to make it onto the governmental agenda, there were policy entrepreneurs in both Ghana and Rwanda. In the former, the Head of the Ghana FDA and the Director for

Technical Coordination in the Ministry of Health were policy entrepreneurs for the AMA treaty signing and ratification process. In Rwanda, a senior member of staff at the Rwanda FDA, Rwanda's Ambassador in Ethiopia, and the President were policy entrepreneurs. It is worth noting that in Rwanda, the key informant stated that the agenda setting process for the AMA treaty's signing and ratification was not the result of one person's work – there were several policy entrepreneurs in different government offices. In terms of policy windows, our study found that the AMA treaty was signed by Ghana in Cairo, Egypt where a meeting was being held by the AU Social Admin bloc where the environment is said to have been appropriate and the moment was seized to sign the treaty. Ghana had also recently been appointed to host the African Continental Free Trade Area Secretariat and this enabled the AMA treaty ratification. This is the 'spill over' concept that Kingdon proposed in his framework. The 'spill over' concept refers to the opening of a policy window triggering the opening of another policy window elsewhere in a related area (89,90). For Rwanda, the window of opportunity to sign and ratify the treaty opened partly due to the President being the Chair of the African Union when the treaty was being endorsed. The President is said to have been the Chair of the AUDA-NEPAD, and he was also pushing for the African Continental Free Trade Area agreement.

5.5 Limitations

Lusophone AU Member States (Angola, Guinea-Bissau, Mozambique, and São Tomé and Príncipe) were excluded from the survey due to lack of capacity to translate the questionnaires and respondents' responses from English to Portuguese and vice versa. Equatorial Guinea was also excluded due to Spanish and Portuguese being the official languages. It is possible that the experiences of these countries that we excluded are different to those of the countries that were included in the survey.

Countries that are not active in the AMRH initiative were also excluded from the survey as the contact details for their Head of NMRA or a designated focal point person were not available in the African Union Development Agency – New Partnership for Africa's Development (AUDA-NEPAD) AMRH database. These

countries are Djibouti, Libya, Malawi, Mauritius, and Sahrawi Republic. The perceived benefits, enabling factors and challenges encountered by these countries in domesticating the AU model law and/or ratifying the AMA treaty would have provided additional or different insights considering that participating in the AMRH initiative is a key facilitator of taking up the harmonisation initiatives under investigation.

Both the process of domestication of the AU Model Law and the ratification of the AMA treaty have to occur within the confines of the national legal system and there are major differences between the English legal system inherited by previous British colonies and the Napoleonic system inherited by previous French, Spanish and Portuguese colonies. However, this study did not examine if the reliance on an Act of Parliament, supplemented by Regulations issued by a Minister of Health, which underpinned the English-style Model Law, is compatible with the reliance on decrees and other instruments that might be more prevalent in a Napoleonic legal system. Additionally, the study did not investigate whether the legal differences alter the way in which ratification is achieved in different countries or if they have any implications for the future operation of the AMA.

Self-administered questionnaires were used in this research study. It is possible that if interviews were conducted instead of using self-administered questionnaires for Part I of this study, other themes may have been found that are consistent with the Consolidated Framework for Implementation Research.

5.6 Summary

In this chapter, the findings of the study were discussed in three parts and comparisons were made between the research findings and the literature. Any similarities between the two were also highlighted. Furthermore, limitations of the research were outlined. The final chapter will conclude the research as a whole and provide recommendations.

CHAPTER SIX

CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

This study sought to analyse in-depth the rationale, perceived benefits, enabling factors and challenges of domesticating and implementing the AU Model Law on Medical Products Regulation by AU Member States and of the establishment of the AMA. The AU Model Law was developed by the AUDA-NEPAD and key stakeholders with the aim of ensuring the promotion of innovation and access to new health technologies (14,15). The goal of this non-prescriptive model legislation is to streamline regulatory systems and facilitate the overall regional harmonisation process (6,9,10,14,15,20,31,53). The AMA will be a specialised agency of the AU with a vision to ensure that all Africans have access to affordable medical products, that meet internationally recognised standards of quality, safety and efficacy, for priority diseases/conditions (3,36,48,59,60).

We found that the perceived benefits of AU Model Law domestication and implementation include the harmonisation of regulatory systems and enabling cooperation with other NMRAs, being in line with regional international standards and best practices, facilitating the exchange of regulatory information, increasing the number of registered medical products, improving the regulation of medical products and technologies, curbing the circulation of SF medical products, and having an NMRA that is fully mandated to conduct regulatory activities. In addition, AU Model Law domestication and implementation is perceived to enable the regulated community to clearly understand their roles, improve transparency and efficiency of the medicines regulatory framework and safety monitoring systems, and for countries with limited resources, it was expressed that domesticating the model law would enable these countries to adopt strong pharmaceutical laws in a rapid manner. Furthermore, the model law is perceived to result in better oversight of clinical trials, increase export opportunities for domestic pharmaceutical manufacturers, increase confidence in the health system and medicines, and reduce antimicrobial resistance. Moreover,

it was voiced that adopting the model law would enable NMRAs to participate in regional and continental harmonisation initiatives, including the AMA. Some of the perceived disadvantages of domesticating the model law include the fact that the process of amending existing Acts is slow and lengthy, harmonisation would result in countries with robust regulatory systems relying on data from those with weak systems and such data might not be up to standard, the expanded mandate brought about by the AU Model Law may not be affordable, and regulated products are not common across the region. Despite these perceived disadvantages, all countries that have implemented the AU Model Law reported that there have been no disadvantages to its implementation.

In this research study, participation in regional and international harmonisation programmes of different communities and development bodies enabled the domestication of the model law. Other enabling factors include the desire to have legal provisions at the national level that allow regional harmonisation and international collaboration, breakthrough movement towards the achievement of WHO maturity level 3 status, presence of advocates, facilitators, or champions, timing, the presence of gaps in the current Act, and the desire to have an appropriate law including all the regulatory functions of a NMRA. Political will and leadership are also considered to be enabling factors for the domestication and implementation of the AU Model Law and so is the availability of both financial and human resources. The challenges or barriers encountered in the process of domesticating and implementing the AU model law include the lack of human and financial resources, lack of political will and competing priorities at the national level, overlapping roles of government institutions, and the process of amending/repealing laws being slow and lengthy.

The AMA is being established by treaty to effectively address some of the challenges that are being faced by African countries. These challenges include countries having different sovereign approaches to their legal and regulatory frameworks, regulatory divergence across borders, inadequate financial resources, gaps in the development of a unified regulatory science body and the lack of a competent regulatory workforce. Ratification of the AMA treaty is

therefore perceived to address these challenges. Our study found that the AMA is expected to be an information sharing agency, to improve access to medical products, strengthen and harmonise regulatory systems on the continent, assist countries establish NMRAs and build national regulatory capacity, and curb the circulation of substandard and falsified medical products in Africa. The AMA is also perceived to enable reliance and recognition mechanisms to be implemented by African NMRAs.

The existence of mature NMRAs, the desire to have harmonised regulatory systems in Africa that allow for collaboration, the presence of strong political will and support from the parent Ministry and the government as well as appropriate advocacy to expedite treaty signing are all enabling factors for the signing of the AMA treaty. The presence of facilitators, advocates, or champions also enables treaty signing and ratification. The challenges encountered in treaty signing include the fact that the process is slow, there is a lack of awareness and limited understanding of the signing of the treaty, and in some countries there is bureaucracy and red tape making it difficult to convince the leaders to sign. Competing national priorities, administrative and legislative procedures, changes in office bearers in the public system and stagnation of the process at the ministerial level are also challenges encountered.

Kingdon's Multiple Streams Framework was used to gain an understanding of the agenda setting process leading to the ratification of the treaty for the establishment of the AMA. We found that African countries face several regulatory challenges that all served as motivators for the establishment of the AMA. In the policy stream, African regulators and health leaders considered the establishment of the AMA by treaty to be a viable solution to address the challenges faced on the continent. The agency's establishment as a solution to reported problems in Africa is also considered to hold promise to build capacity on the continent, result in timely access to medical products, as well as create harmonised medicines regulatory systems in Africa that can share risks. In the politics stream, the presence of political will and leadership, the desire to be pioneers in taking up continental initiatives, and actively participating in the

development of the treaty for the establishment of the AMA led to ratification of the treaty as a policy solution for Africa's medicines regulatory problems. The three separate streams then came together which allowed the AMA treaty to make it onto the governmental agenda. The coupling of the streams was done by policy entrepreneurs in both Ghana and Rwanda. Policy windows then opened for both countries which allowed the treaty to be ratified and the ratification instruments were deposited at the African Union Commission.

It was important to conduct this research on the domestication and implementation of the AU Model Law as part of monitoring and evaluation of the AMRH Strategic Framework, and to interrogate progress to date of the establishment of the African Medicines Agency, as it directly impacts regional, continental and global frameworks and goals. This research, which met all its objectives, has provided well-founded, scientific and evidence-based results that can be used for policy synthesis. The AU Model Law and the AMA hold promise to address gaps and inconsistencies in national regulatory legislation as well as ensure effective medicines regulation by galvanising technical support, regulatory expertise and resources at a continental level. African people must have access to essential medical products and health technologies that are quality-assured, safe, efficacious and affordable as part of Agenda 2063 efforts.

6.2 Recommendations

Based on the findings of this research study, the following recommendations are made:

Governments should fast track the process of amending existing Acts to incorporate key components of the AU Model Law. They should also provide technical and financial support to their NMRAs and African medicines regulatory harmonisation initiatives.

Governments should demarcate roles, duties and responsibilities of institutions in order to avoid any overlaps. Any legislations and regulations that also contradict each other must be amended or repealed.

African NMRAs must participate in regional and international harmonisation programmes of different communities and development bodies (e.g., WHO-PQ, WHO-CRP, Swissmedic MAGHP) as this is an enabler for AU Model Law domestication and implementation. It also provides an opportunity for African regulators to improve their regulatory expertise and capacity.

In countries that are yet to sign and/or ratify the AMA treaty, facilitators, advocates and champions must be identified and equipped with information and resources to advocate for these processes to occur. The African Union, AUDA-NEPAD, RECs and development partners must continue to lobby and encourage AU Member States that are yet to sign and/or ratify the treaty to expedite their internal processes in order for the AMA to have membership from all African countries. NMRAs and patient organisations should be involved in the advocacy work and decision making processes as they are key stakeholders that can enable the process.

This study found that it is believed by some NMRA staff that the AMA will result in loss of autonomy and revenue for national and regional authorities. It was also stated that once the AMA is established and AU Member States have signed and ratified the treaty, there will be a requirement for financial contribution which will be a burden on the already overstretched country budgets. Therefore, we recommend that the AMA's shape, role and governance structure be clearly stated and communicated to NMRAs and AU Member States in order to address any ambiguities about the scope and mandate of the AMA. The AMA should also have sustainable financing mechanisms that do not place a burden on member states and NMRAs.

Another concern that was raised in this study by small countries with limited regulatory capacity is that they may not be considered equals in the AMA when it becomes operational. There is a fear that the AMA will cater more for countries with robust regulatory systems and those with lower maturity levels will continue to be left behind. Therefore, the AMA should have a fair, transparent system and regional representativeness in the selection and appointment of experts/consultants. It should also equitably cater for the needs of small countries

and countries with limited regulatory capacity. Additionally, it must have transparent good practices in reaching decisions on recommending products and independence from foreign governments and development partners with ulterior motives.

Once the AMA is operational, there should be no duplication of effort by NMRA, regional regulatory harmonisation initiatives and the continental regulator.

The AMA should foster an environment that is conducive for innovation and the biopharmaceutical industry in order to improve access to quality-assured, safe and efficacious medical products for Africans.

6.2.1 Recommendations for further research

- A comparative study between the AMA initiative and other continental initiatives should be done in order to draw lessons from their implementation and find areas of applicability to Africa.
- A study should be done to obtain the pharmaceutical industry's viewpoints and expectations of the African Medicines Agency as they are the regulated community.

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Appendix I
AU Member States

The AU is made up of 55 Member States which represent all the countries on the African continent. AU Member States are divided into five geographic regions which were defined by the OAU in 1976 (CM/Res.464QCXVI). The following list shows all members states grouped by region, in alphabetical order, and their date of joining the AU or its predecessor the OAU.

Source: https://au.int/en/member_states/countryprofiles2

- **Central Africa**

Member State	**Abbreviation**	**Date of joining the OAU or AU**
Republic of Burundi	Burundi	25 May 1963
Republic of Cameroon	Cameroon	25 May 1963
Central African Republic	Central African Republic	25 May 1963
Republic of Chad	Chad	25 May 1963
Republic of the Congo	Congo Republic	25 May 1963
Democratic Republic of Congo	DR Congo	25 May 1963
Republic of Equatorial Guinea	Equatorial Guinea	12 October 1968
Gabonese Republic	Gabon	25 May 1963
Democratic Republic of São Tomé and Príncipe	São Tomé and Príncipe	18 July 1975

- **Eastern Africa**

Member State	**Abbreviation**	**Date of joining the OAU or AU**
Union of the Comoros	Comoros	18 July 1975
Republic of Djibouti	Djibouti	27 June 1977
State of Eritrea	Eritrea	24 May 1993

Federal Democratic Republic of Ethiopia	Ethiopia	25 May 1963
Republic of Kenya	Kenya	25 May 1963
Republic of Madagascar	Madagascar	25 May 1963
Republic of Mauritius	Mauritius	August 1968
Republic of Rwanda	Rwanda	25 May 1963
Republic of Seychelles	Seychelles	29 June 1976
Federal Republic of Somalia	Somalia	25 May 1963
Republic of South Sudan	South Sudan	27 July 2011
Republic of the Sudan	Sudan	25 May 1963
United Republic of Tanzania	Tanzania	25 May 1963
Republic of Uganda	Uganda	25 May 1963

- **Northern Africa**

Member State	**Abbreviation**	**Date of joining the OAU or AU**
People's Democratic Republic of Algeria	Algeria	25 May 1963
Arab Republic of Egypt	Egypt	25 May 1963
Libya	Libya	25 May 1963
Islamic Republic of Mauritania	Mauritania	25 May 1963
Kingdom of Morocco	Morocco	1963/31 January 2017
Sahrawi Arab Democratic Republic	Sahrawi Republic	22 February 1982
Republic of Tunisia	Tunisia	25 May 1963

❖ **Southern Africa**

Member State	**Abbreviation**	**Date of joining the OAU or AU**
Republic of Angola	Angola	11 February 1975
Republic of Botswana	Botswana	31 October 1966
Kingdom of Eswatini	Eswatini	24 September 1968
Kingdom of Lesotho	Lesotho	31 October 1966
Republic of Malawi	Malawi	13 July 1964
Republic of Mozambique	Mozambique	18 July 1975
Republic of Namibia	Namibia	June 1990
Republic of South Africa	South Africa	6 June 1994
Republic of Zambia	Zambia	16 December 1964
Republic of Zimbabwe	Zimbabwe	18 June 1980

❖ **Western Africa**

Member State	**Abbreviation**	**Date of joining the OAU or AU**
Republic of Benin	Benin	25 May 1963
Burkina Faso	Burkina Faso	25 May 1963
Republic of Cabo Verde	Cabo Verde	18 July 1975
Republic of Côte d'Ivoire	Côte d'Ivoire	25 May 1963
Republic of the Gambia	Gambia	9 March 1965
Republic of Ghana	Ghana	25 May 1963
Republic of Guinea	Guinea	25 May 1963
Republic of Guinea-Bissau	Guinea-Bissau	19 November 1973

Republic of Liberia	Liberia	25 May 1963
Republic of Mali	Mali	25 May 1963
Republic of Niger	Niger	25 May 1963
Federal Republic of Nigeria	Nigeria	25 May 1963
Republic of Senegal	Senegal	25 May 1963
Republic of Sierra Leone	Sierra Leone	25 May 1963
Togolese Republic	Togo	25 May 1963

Appendix II

A. Covering Letter

The Head of Agency,

REF: Introductory letter to Heads of National Medicines Regulatory Authorities.

This letter serves to discuss your National Medicines Regulatory Authority's possible participation in a research study focused on the implementation of the African Union (AU) Model Law on Medical Products Regulation and the establishment of the African Medicines Agency (AMA). The study is a census survey and Heads of National Medicines Regulatory Authorities and their Chief Regulatory Officers (or the equivalent position) of all 55 AU Member States are being invited to participate. The research study, and participating in the research, has no foreseeable risk.

The AMA, which was expected to be launched in 2018, is to be established by treaty and will, as one of its mandates, coordinate the regional harmonisation systems that are enabled by AU Model Law domestication and implementation. At the national level, the implementation targets related to the AU Model Law were to have at least 25 countries domesticating the AU Model Law by 2020. However, the implementation targets for the AU Model Law have not been fully met, and no research has been conducted on the motivation of the individual AU Member States to domesticate and implement the model law, or on the enabling factors and challenges involved. The same is true for the signing and ratification of the AMA treaty. Moreover, by examining the experiences and agenda setting processes of the AU Member States that have ratified the AMA treaty we potentially draw important lessons for countries attempting to sign and ratify the AMA treaty. Therefore, this research aims to add to the scientific body of knowledge in this regard by carrying out an in-depth analysis of these subject matters using a survey study design.

Ethical approval for this research has been obtained from the University of the Western Cape Humanities and Social Science Research Ethics Committee (HSSREC). Please find attached consent forms and the accompanying questionnaires which must be completed by you, the Head of the NMRA, and your Chief Regulatory Officer or another person you deem to be suitable and capable to provide the requested information. Participation in this research is voluntary and participants are free to leave any questions unanswered. Participants can also withdraw from the study at any stage.

If you want to discuss this research further, please feel free to contact us.

Sincerely,

Kim Ward (PhD)	Bakani Ncube
Research Supervisor	MPharm Candidate

Appendix II

B. Consent Form

CONSENT TO PARTICIPATE IN RESEARCH

Purpose and Background

Bakani Mark Ncube, Prof. Admire Dube and Prof. Kim Ward from the University of Western Cape, School of Pharmacy, are conducting research on the domestication and implementation of the African Union (AU) Model Law on Medical Products Regulation and the establishment of the African Medicines Agency (AMA). This research is for a Masters thesis of the candidate and the research study, and participating in the research, has no foreseeable risk.

The AMA, which was expected to be launched in 2018, is to be established by treaty and will, as one of its mandates, coordinate the regional harmonisation systems that are enabled by AU Model Law domestication and implementation. At the national level, the implementation targets related to the AU Model Law are to have at least 25 countries domesticating the AU Model Law by 2020. However, the implementation targets for the AU Model Law have not been fully met, and no research has been conducted on the motivation of the individual AU Member States to domesticate and implement the model law, or on the enabling factors and challenges involved. The same is true for the signing and ratification of the AMA treaty. In addition, by examining the experiences and agenda setting processes of the AU Member States that have ratified the AMA treaty we potentially draw important lessons for countries attempting to sign and ratify the AMA treaty. Therefore, this research aims to add to the scientific body of knowledge in this regard by carrying out an in-depth analysis of these subject matters. In spite of the challenges, the AU Model Law and the AMA hold promise to address gaps and inconsistencies in national regulatory legislation as well as ensure effective medicines regulation by galvanising technical support, regulatory expertise and resources at a continental level.

Procedures

If you agree to participate in this research, you will be asked to complete a questionnaire on the domestication and implementation of the AU Model Law and the signing of the treaty for the establishment of the African Medicines Agency, and have 4 weeks to do so. The questionnaire will be returned to the investigator for analysis, and responses will only be used for research purposes. Your name will not be used on the questionnaire or on other printed materials associated with the study. Any publications or presentations of the findings from this study will not include personally identifying information.

Consent

A copy of this consent form will be given to you to keep. Participation in this research is voluntary and you are free to leave any questions unanswered. You can also withdraw from the study at any stage. If you consent to participate in this study, please sign below:

I…… (Full names of participant) hereby confirm that I understand the contents of this document and the nature of the research project, and I consent to participating in the research project.

I understand that I am at liberty to withdraw from the project at any time, should I so desire.

SIGNATURE OF PARTICIPANT DATE

…… ……

Appendix II

Appendix III
The Domestication & Implementation of the African Union (AU) Model Law on Medical Products Regulation

Background

The African Union (AU) Model Law on Medical Products Regulation, hereafter referred to as the AU Model Law, was developed by the African Union Development Agency New Partnership for Africa's Development (AUDA-NEPAD) and key stakeholders. The history of the AU Model Law is that the draft law was developed through the African Medicines Regulatory Harmonisation (AMRH) initiative platform and endorsed by the Pan African Parliament Committee on Health, Labour and Social Affairs. In November 2015, the AU technical committee on Justice and Legal Affairs approved the AU Model Law which is now available for use as a starting point for the establishment of regulatory bodies and providing support for legislation in AU Member States. In January 2016, the AU Model Law was then endorsed at the AU Summit in Addis Ababa, Ethiopia by the AU Heads of State and Government. Following endorsement, next steps taken were to engage with Regional Economic Communities (RECs), Regional Organisations (ROs), and AU Member States to update and enact regional legal frameworks and national laws on the regulation of medical products. This research therefore aims to analyse in-depth the rationale, (perceived) benefits and in-country processes of domesticating and implementing the AU Model Law. In addition, it aims to determine the enabling factors and challenges/barriers encountered by AU Member States in the domestication and implementation of the AU Model Law.

The Domestication & Implementation of the AU Model Law in AU Member States Questionnaire	
1. AU Member State: Click here to enter text.	**2. Name of National Medicines Regulatory Authority (NMRA)/the equivalent:** Click here to enter text.
3. Is there legislation for medical products regulation in your country? Choose an item.	
4. What is the title of the legislation for medical products? Click here to enter text.	
5. In what year did the legislation stated in Question 4 first come into effect? Click here to enter text.	
6. In what year was the legislation stated in question 4 last updated? Click here to enter text.	
7. What was the reason for and motivation to update the legislation?	Click here to enter text.
8. Has your country domesticated[1] the AU Model Law?	Choose an item.

9. If the response to question 8 is Yes, what was the date of domestication of the model law?	Click here to enter a date.
10. If the response to question 8 is No, does your country intend to or have an interest in domesticating and implementing the AU model law?	Choose an item.
11. If the response to question 10 is No, why not?	Click here to enter text.
12. Please indicate if the AU Model Law was (/will be) partially[2] or fully[3] domesticated.	Choose an item.
13. If the response to question 12 was 'Partially', please indicate which components of the AU Model Law were (/will be) domesticated	☐ Establishment of a National Medicines Regulatory Authority (NMRA) ☐ Consideration of Applications for Marketing Authorisation ☐ Licensing of Manufacturers, Importers, Exporters, Wholesalers and Distributors ☐ Establishment of an Administrative Appeals Committee ☐ Post-Marketing Surveillance and Safety Monitoring ☐ International Cooperation and Harmonisation of Regulation of Medical Products ☐ Regulatory Inspection and Enforcement ☐ Control of Clinical Trials of Medical Products ☐ Control of Promotion and Advertising of Medical Products ☐ Quality Control Laboratory ☐ Scheduling, Classification and Control of Medical Products
14. In your country, what is the reason	Click here to enter text.

for this partial/or full domestication	
15. Has your country implemented[4] the AU Model Law?	Choose an item.
16. What is the process in your country for domesticating and implementing the AU Model Law? Who are the actors involved and what are their roles?	Click here to enter text.
17. What were (/are) the perceived benefits of domesticating and implementing the AU Model Law?	Click here to enter text.
18. What were (/are) the perceived disadvantages of domesticating and implementing the AU Model Law?	Click here to enter text.
19. Were (/Are) there internal (i.e. within the NMRA) facilitators, advocates, or champions in the process of domesticating and implementing the AU Model Law? Who are they and what role have they played?	Click here to enter text.
20. Were (/Are) there external (i.e. outside the NMRA e.g. Ministry of Health, AUDA-NEPAD, Regional Economic Community, etc.) facilitators, advocates, champions in the	Click here to enter text.

process of domesticating and implementing the AU Model Law? Who are they and what role have they played?	
21. In your country, what were (/are) the enabling factors that allow for the domestication and implementation of the AU Model Law?	Click here to enter text.
22. What were (/are) the challenges or barriers encountered in the domestication and implementation of the AU Model Law?	Click here to enter text.
23. What solutions were (/are being) considered or put in place to overcome the challenges or barriers stated in question 22	Click here to enter text.
24. If the AU Model Law has been implemented, has your NMRA started accruing benefits from this implementation[4]?	Choose an item.
25. If the response to question 24 is Yes, what are these benefits that have been accrued?	Click here to enter text.
26. If the response to question 15 is Yes, has there been a downside to implementing the AU Model Law?	Click here to enter text.

(Question 15 = Has your country implemented[4] the AU Model Law?)	
Any other comments or additional details you wish to provide on the domestication and implementation of the AU Model Law in your country:	Click here to enter text.

Definitions of Key Terms

[1]AU Model Law Domestication: the process of adapting (or adopting it as is) the AU Model Law so that it is consistent with a country's constitutional principles and legal system, which may include amending or repealing any national laws that are inconsistent

[2]Partial AU Model Law Domestication: the process of incorporating some provisions from the AU Model Law which are not in a country's existing legislation

[3]Full AU Model Law Domestication: the process of incorporating all provisions from the AU Model Law into a country's legislation

[4]AU Model Law Implementation: the use of the new law that incorporates some or all provisions of the AU Model Law in a country following approval by Parliament and publication in the respective government gazette.

Appendix IV
THE SIGNING OF THE TREATY FOR THE ESTABLISHMENT OF THE AFRICAN MEDICINES AGENCY

Background

The establishment of African Medicines Agency (AMA) is based on the African Union (AU) Executive Council Decision EX.CL/Dec.857 (XXVI) of January 2015. The AMA is to be established through a treaty which takes into consideration key AU decisions, declarations and policy frameworks including the 55th Decision of the AU {Assembly/AU/Dec.55(IV)} taken during the 2005 Abuja Summit and the 19th Ordinary Session Decision of the Assembly {Assembly AU/Dec.442(XIX)}. On 11 February 2019, the AU Assembly, during their 32nd Ordinary Session in Addis Ababa, Ethiopia, adopted the treaty for the establishment of the AMA. This treaty was then unanimously adopted by the African Ministers of Health gathered at the 71st World Health Assembly in Geneva.

In the context of moving towards AMA's establishment, the AMA treaty must be signed and then ratified by AU Member States. However, the AMA treaty has not been ratified by the required minimum of 15 countries. This research therefore aims to analyse in-depth the rationale, (perceived) benefits and in-country processes of signing and ratifying the AMA treaty. In addition, it aims to determine the enabling factors and challenges/barriers encountered by AU Member States in signing and ratifying the AMA treaty.

The Signing of the Treaty for the Establishment of the African Medicines Agency Questionnaire	
1. AU Member State: Click here to enter text.	**2. Name of National Medicines Regulatory Authority (NMRA)/the equivalent:** Click here to enter text.
3. Has your country signed the treaty for the establishment of the African Medicines Agency? Choose an item.	
4. If the response to question 3 is No, does your country intend to sign and ratify the treaty for the establishment of the African Medicines Agency? Choose an item.	
5. If the response to question 4 is No, why does your country not intend to sign and ratify the treaty for the establishment of the African Medicines Agency? Click here to enter text.	
6. What are the perceived advantages of the establishment of the African Medicines Agency to your country? Click here to enter text.	
7. What are the perceived disadvantages of the establishment of the African Medicines Agency to your country? Click here to enter text.	
8. What is your NMRA's expectation of the	Click here to enter text.

African Medicines Agency?	
9. What is your NMRA's perception of its role and contribution to/in AMA?	Click here to enter text.
10. In your country, what is the process to sign and ratify the treaty for the establishment of the African Medicines Agency? Who are the actors involved and what are their roles?	Click here to enter text.
11. Are there (/were there) internal (i.e. within the NMRA) facilitators, advocates, or champions for the signing of the treaty for the establishment of the African Medicines Agency? Who are (/were) they and what is (/was) their role?	Click here to enter text.
12. Are there (/were there) external (i.e. outside the NMRA e.g. Ministry of Health, AUDA-NEPAD, Regional Economic Community, etc.) facilitators, advocates, or champions for the signing of the treaty for the establishment of the African Medicines Agency? Who are (/were)	Click here to enter text.

they and what is (/was) their role?	
13. In your country, what are (/were) the enabling factors that allow for signing of the treaty for the establishment of the African Medicines Agency?	Click here to enter text.
14. What are (/were) the challenges or barriers encountered in signing the treaty for the establishment of the African Medicines Agency?	Click here to enter text.
15. What solutions are being (/were) considered or put in place to overcome the challenges or barriers stated in question 14?	Click here to enter text.
16. If the response to question 3 was Yes, has your country ratified the treaty for the establishment of the African Medicines Agency? *(Question 3 = Has your country signed the treaty for the establishment of the African Medicines Agency?)*	Choose an item.
17. If the response to question 16 is No, what are the challenges and/or barriers currently being faced in transitioning from having signed the	Click here to enter text.

treaty to having the treaty ratified?	
Any other comments or additional details you wish to provide on the signing and/or ratification of the treaty for the establishment of the African Medicines Agency:	Click here to enter text.

Definitions

[1] Signing the AMA treaty: an expression of intention by a country to comply with the treaty. However, this expression of intent in itself is not binding.

[2] Ratification of the AMA treaty: the national procedure where the AU Member State puts in place a law that allows for the implementation of the AMA treaty. The treaty is now officially binding on the state.

Appendix V
THE AGENDA SETTING PROCESS LEADING TO THE RATIFICATION OF THE TREATY FOR THE ESTABLISHMENT OF THE AFRICAN MEDICINES AGENCY.

The establishment of African Medicines Agency (AMA) is based on the African Union (AU) Executive Council Decision EX.CL/Dec.857 (XXVI) of January 2015. The AMA is to be established through a treaty which takes into consideration key AU decisions, declarations and policy frameworks including the 55th Decision of the AU {Assembly/AU/Dec.55(IV)} taken during the 2005 Abuja Summit and the 19th Ordinary Session Decision of the Assembly {Assembly AU/Dec.442(XIX)}. On 11 February 2019, the AU Assembly, during their 32nd Ordinary Session in Addis Ababa, Ethiopia, adopted the treaty for the establishment of the AMA. This treaty was then unanimously adopted by the African Ministers of Health gathered at the 71st World Health Assembly in Geneva. In the context of moving towards the AMA's establishment, the AMA treaty must be signed and then ratified by AU Member States. However, the AMA treaty has not been ratified by the minimum required number of countries for its establishment. By examining the experiences of the 5 countries that had successfully ratified the AMA treaty by September 2020, important lessons can be drawn from them for other countries that intend to sign and/or ratify the AMA treaty. Therefore, this research aims to examine the agenda-setting process leading to the ratification of the treaty for the establishment of the AMA, using AU Member States that have done so as case studies.

Interview Guide

1. What was the motivation to sign and ratify the treaty for the establishment of the African Medicines Agency?
2. Were there any perceived disadvantages of establishing the African Medicines Agency?
3. What was the process for the signing and ratification of the treaty for the establishment of the African Medicines Agency? Who were the (internal and external) actors involved and what were their roles?
4. What were the other activities, initiatives or agenda items being considered by decision makers at the time when the signing and ratification of the AMA treaty was also being considered?
5. What was the AMA treaty's priority level relative to the priority level of the other activities, initiatives or agenda items? Why do you think the AMA treaty had this priority level?

6. What opportunity presented itself that enabled the treaty to be ratified amidst other governmental agenda items and priorities?
7. Were there facilitators/advocates/champions in the processes of signing and ratifying the treaty for the establishment of the African Medicines Agency? Who were they and what role did they play?
8. What were the facilitators/enabling factors that led to the signing and ratification of the treaty for the establishment of the African Medicines Agency?
9. What were the challenges/barriers encountered in signing and ratifying the treaty for the establishment of the African Medicines Agency?
10. How were these challenges/barriers overcome?
11. How did the country manage to successfully transition from having signed the treaty to having the treaty ratified?