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EVALUATION OF MEDICINES REGULATORY INTERVENTIONS IN THE EAST AFRICAN COMMUNITY REGION



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DECLARATION

I, Margareth Ndomondo-Sigonda, declare that this thesis, is my own unaided work. It is submitted in fulfilment of requirement of the degree of Doctor of Philosophy (PhD) at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or any examination in this or any other University.



Margareth Ndomondo-Sigonda

14 day of May 2021 in Johannesburg

DEDICATION

This thesis is dedicated to my husband Guido Gregory Sigonda; and my children Germaine, Gertrude and Graham, for always encouraging me throughout this journey.

PUBLICATIONS:

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ABSTRACT

The study assessed the effect of the Medicines Regulatory Harmonization (MRH) initiative in improving regulatory capacity in the East African Community (EAC) Partner States. An exploratory mixed-method design using both qualitative and quantitative data, was employed. Data was collected from six National Medicines Regulatory Authorities (NMRAs) and the EAC Secretariat through a combination of semi-structured interviews, questionnaires, and checklists for the period 2011/12-2014/15 while 2010/11 data served as baseline. Interviews were conducted with heads of agencies; regulatory and monitoring and evaluation experts; and the EAC Seretariat Project Officer. NMRAs performance was measured using a set of 29 indicators grouped into 9 categories. In addition, document review using published reports, grey literature and media articles was conducted. Collaboration, harmonization, joint dossier reviews and inspections of manufacturing sites; reliance and cooperation were identified as key factors for building trust and capacity among NMRAs. Results show that 83.3% of the EAC Partner States have comprehensive medicines laws with autonomous NMRAs. All the NMRAs have functional registration and inspection systems for pharmaceutical manufacturing sites. They all use regional harmonised guidelines for registration, inspection, quality management and information management system. 80% of the NMRAs have attained ISO:2015 certification. Efficiency of registration processes has improved by 66.6% Industry concerns on joint review process; transparency; and accountability are areas to be addressed by EAC NMRAs. Different financing models are used to regulate pharmaceutical markets in the region with Burundi NMRA relying on government funding while others use a combination of sources of revenue. Zanzibar NMRAs is financed through government (50.40%), industry fees (40.60%) and donors/other sources (9%). For Tanzania-Mainland; the industry fees contribution increased from 60% ($2,018,608.88) in 2011 to 86% ($8,123,093) in 2015 with Government contributing on average 19.60% ($1,168,299.09) over the studied period. The Ugandan NMRA depends 98.25% on industry fees ($8,077,238.20). The indicators generated out of this research can be replicated for evaluation of similar initiatives across and beyond the African continent and contribute to public health policy.

Key words: medical products regulatory capacity, regional harmonization in Africa, collaboration, cooperation, efficiency, transparency, sustainability, East African Community, governance, NMRA financing.

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STRUCTURE OF THE THESIS

This PhD is being written through a publication route, with the thesis consisting of four published papers.

The first publication titled “Medicines Regulation in Africa – Current State and Opportunities’, is an in-depth analysis of the status of medicines regulatory systems in Africa [15]. This paper draws upon original research, published reports and data from the AUDA-NEPAD and the World Health Organization (WHO), including the WHO Pharmaceutical Sector Profiles and Country Reports, as well as policy statements and documentation, to provide an overarching summary of national medicines regulatory authorities (NMRAs) in Africa.The paper provides information on the status of NMRAs in Africa as basis for identifying gaps and existing opportunities for improving regulatory capacity, promoting public health and advancement of pharmaceutical industry. The paper looks at 54 African Union Member States regulatory capacities focusing on organizational setup and management systems; policy and legal frameworks; the core regulatory functions performed; and the NMRAs participation in harmonization efforts.

The second paper titled “The African Medicines Regulatory Harmonization Initiative: Progress to Date”; provides insight on the genesis of the initiative and progress attained so far [16]. The paper describes the regulatory situation before and after inception of the AMRH Initiative including progress on harmonization of registration requirements and joint assessment of dossier applications by participating countries through the African Union (AU) recognized regional economic communities (RECs). The benefits of domestication of the AU Model Law on Medical Products Regulation and efforts to accelerate the fight against sub-standard and falsified medical products are elaborated in this paper. Approaches to institute sustainable regulatory capacity development programmes and the contribution of the eleven (11) Regional Centres of Regulatory Excellence (RCOREs) in increasing Africa’s regulatory workforce are explained. The paper further highlights the contribution of the AMRH Initiative in reducing marketing authorization timelines in East African Community (EAC) and the Southern African Development Community (SADC) member states. It also highlights challenges faced by

NMRAs in using the outcome of the regional joint dossier review for national decision-making processes.

A third publication is titled “National Medicines Regulatory Authorities Financial Sustainability in the East African Community” [92]. This paper provides a synthesis of the various NMRAs funding options in five EAC study countries namely Burundi, Kenya, Rwanda, Tanzania (Mainland and Zanzibar) and Uganda. The EAC research on NMRA funding indicates that government and industry fees are the main sources of funding while donor contribution is insignificant. Government policy, legal framework, and fee’s structure are the key enablers of NMRAs financial sustainability.

A fourth publication is titled “Harmonization of medical products regulation: A key factor for improving regulatory capacity in the East African Community” [93]. This paper analyses how the EAC regulatory harmonization initiative has contributed to improving NMRAs capacity focusing on registration and inspection of manufacturing sites. The paper further advocates for use of indicators tool developed from this research to assess performance of regional harmonization initiatives across and beyond the African continent and contribute to public health policy.

The EAC research forms the first part of this thesis while the four publications derived from literature review and research work comprise the second part of the thesis. There are four chapters of the EAC research paper. The first chapter provides a literature review, background, aims and objectives including the research hypothesis. Chapter two focuses on study design and methodology including the development of the indicators’ metrics, data collection and analysis. The results of this research are provided in Chapter three and are grouped in nine (9) categories namely policy and legal frameworks; regulatory governance; NMRA financing; medicines registration and inspection; information management systems and quality management systems. Other results areas include partnerships and coordination; level of transparency and accountability and mutual recognition framework. Discussion, recommendations and conclusions are provided in Chapter four of the thesis.

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LIST OF ACRONYMS

ABREMA	Drug and Food Regulatory Authority of Burundi
ACCESS	Drug Registration Software Solutions
AFDRAN	African Drug Regulatory Authorities Network
AMA	African Medicines Agency
AMQF	African Medicines Quality Forum
AMRH	African Medicines Regulatory Harmonization Initiative
API	Active Pharmaceutical Ingredient
AU	African Union
AUC	African Union Commission
AUDA-NEPAD	African Union Development Agency - New Partnership for Africa's Development
AVAREF	African Vaccines Regulatory Forum
BMGF	Bill and Melinda Gates Foundation
CHAI	Clinton Health Access Initiative
CHMP	Committee for Medicinal Products for Human Use
CVMP	Committee for Medicinal Products for Veterinary Use
CIRS	Centre for Innovation in Regulatory Science
CNF	Committee on National Formulary
CSSC	Christian Social Services Commission
CTD	Common Technical Document
DPML	Directorate of Pharmacy, Medicines and Laboratory

EAC	East African Community
ECCAS	Economic Community of Central African States
ECOWAS	Economic Community of West Africa States
e-CTD	Electronic Common Technical Document
EEA	European Economic Area
EGPAF	Elizabeth Glaser Pediatrics AIDS Foundation
EMA	European Medicines Agency
EU	European Union
FFP	Finished Pharmaceutical Formulation
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GDP	Gross Domestic Product
GIZ	German Corporation for International Cooperation
GMP	Good Manufacturing Practice
GRevP	Good Review Practice
GVP	Good pharmacovigilance practice
IAEA	International Atomic Energy Agency
ICH	International Council on Harmonization of Technical Requiremets for Registration of Pharmaceuticals for Human Use
IGAD	Intergovernmental Authority on Development
ISO	International Standards Organization
IMS	Information Management System
JSI	John Snow Inc.

KPPB	Kenya Pharmacy and Poisons Board
LMIC	Low- and Middle-Income Countries
MA	Marketing Authorization
MDGs	Millennium Development Goals
MoH	Ministry of Health
MoU	Memorandum of Understanding
MSH	Management Sciences for Health
NDA	Uganda National Drug Authority
NDQCL	National Drug Quality Control Laboratory
NEPAD	New Partnership for Africa's Development
NMP	National Medicine Policy
NMRA	National Medicines Regulatory Agencies
NOMCOL	A Network of Official Medicines Quality Control Laboratories
MCAZ	Medicines Control Authority of Zimbabwe
OECD	Organization for Economic Co-operation and Development
OpERA	Optimizing Efficiencies in Regulatory Agencies
PMPA	Pharmaceutical Manufacturing Plan for Africa
QMS	Quality Management System
RECs	Regional Economic Community
RFDA	Rwanda Food and Drug Authority
RHO	Regional Health Organizations
SADC	Southern African Development Community
SDGs	United Nations Sustainable Development Goals

SIAMED	WHO Model System for Computer-assisted Drug Registration
SoPs	Standard Operating Procedures
SRAs	Stringent Regulatory Authorities
TFDA	Tanzania Food and Drugs Authority
TMDA	Tanzania Medicine and Medical Devices Authority
TGA	Therapeutic Goods Administration of Australia
TMEA	Trademark East Africa
UHC	Universal Health Coverage
UNECA	United Nations Economic Commission for Africa
UNICEF	The United Nations Children's Fund
UNIDO	United Nations Industrial Development Organization
USP	United States Pharmacopoeia
WB	World Bank
WHO	World Health Organization
WHO-GBT	World Health Organization Global Benchmarking Tool for evaluation of national regulatory systems
WHO-PQ	World Health Organization Pre-Qualification Programme
Zazibona	Zambia, Zimbabwe, Botswana and Namibia collaborative procedure on registration of medicines
ZFDA	Zanzibar Food and Drugs Agency
ZFDB	Zanzibar Food and Drugs Board

PART I

CHAPTER 1: BACKGROUND

1.1 INTRODUCTION

This chapter has 8 sections including the introduction section. The 2nd section is a literature review which analyses the potential of the pharmaceutical industry in Africa in advancing socio-economic development agenda. The section further elaborates how sound regulatory systems and harmonization efforts play a role in optimizing pharmaceutical markets in support of continental and global policy frameworks on access to quality, safe and efficacious health products. The 3rd section is an overview of the East African Community (EAC) as an intergovernmental body including its governance structures and instruments used to advance its development agenda. The 4th section provides information on the EAC medicines regulatory harmonization initiative, its genesis and eventual launch in 2012. Sections 5, 6, 7, and 8 focus on problem statement, aims of the research, research objectives, and research hypothesis, respectively.

1.2 LITERATURE REVIEW

The high disease burden and high mortality from preventable and curable diseases that Africa faces is largely attributed to inadequate health systems, scarce financial and human resources and limited access to good quality, safe and efficacious medicines [1,2]. The latter is further attributed to the lack of a reliable local pharmaceutical manufacturing base and weak medicines regulatory systems, among other factors [3]. In recognition of this problem, the Heads of State and Government of the African Union (AU) in 2005 mandated the formulation of the Pharmaceutical Manufacturing Plan for Africa (PMPA) with a view to

strengthen Africa's ability to produce high quality and affordable medicines that will contribute to improved health and economic outcomes [3]. Another key policy framework that came into force in 2019 is the African Continental Free Trade Area (AfCFTA) which serves as an impetus for boosting intra-African trade through a single market of 1.2 billion people and a cumulative gross domestic product (GDP) of over $3.4 trillion across the 55 member states of the African Union (AU) [4][5].

The value of the health care and wellness sector in Africa is estimated to reach $259 billion by 2030 and the African pharmaceutical market is projected to reach $45 billion by 2020, which is attributed to the changing economic profiles, rapid urbanization, increased healthcare spending and investment, and the increasing incidence of chronic lifestyle diseases [6,7]. Population and economic growth as well as raising consumer awareness is also attributed to the increasing demand of medicines in Africa thus compelling governments and partners' investments in local production and effective regulation of medical products [5,8]. NMRAs play a vital role in assuring the quality, safety and efficacy of medical products including vaccines, blood products, diagnostics and medical devices, which are critical for effective healthcare delivery in a country [9]. Sound, efficient, effective and transparent regulatory systems are important for the promotion of investment in the pharmaceutical sector and socioeconomic advancement [10].

For many years the capacity to regulate medicine in Sub-Saharan African countries has been confronted with fragmented legal frameworks, weak management structures and processes, and a severe lack of staff and resources with subsequent proliferation of substandard and falsified medicines in various markets [11-12]. Seven percent (7%) of the 46 sub-Saharan African countries have been reported to have moderately developed medicine regulatory capacity, about 63% have minimal capacities while the remaining 30% do have NMRA's in place [12]. Poor inspection practices; ineffective licensing and product registration systems; inadequate access to quality control laboratories; non-existent pharmacovigilance, clinical trials oversight and drug promotion control systems are some of the factors which have led to 30% product quality failure rates [13]. This is coupled with inadequate communication and information exchange systems, a lack of transparency and accountability and conflict of

interest [13]. Another study revealed that except for the Sahrawi Republic, all the remaining 53 countries have NMRAs with varying organizational setup and level of functionality operating either as units, departments or as autonomous agencies within Ministries of Health [14].

Effective and efficient regulation of medical products provides an opportunity for investment in manufacturing, trade and sale of pharmaceutical products; and increased research and development of new medical products and technologies; with consequent social and economic benefits to the patients [15–17]. Building medical products regulatory capacity is also crucial for achieving Universal Health Coverage (UHC) goals; the African Union (AU) Agenda 2063 aspirations and goals 1 and 3; as well as Sustainable Development Goals (SDGs) on access to quality, safe and efficacious health products to the people [18].

In recognition of the important role the NMRAs play in advancing public health and economic development, the African Medicines Regulatory Harmonization (AMRH) Initiative was launched in 2009 as part of the AU PMPA framework, to strengthen regulatory capacity, encourage harmonization of regulatory requirements and expediting patients' access to medicines that meet internationally acceptable standards of quality, safety and efficacy [18-20]. Through the AMRH Initiative, countries in the East African Community (EAC) and the Southern African Development Community (SADC) using the Zambia, Zimbabwe, Botswana and Namibia (Zazibona) collaborative procedure, have recorded significant improvements in registration timelines from the average 2-7 years to a median of 7 months [22-28,30-32]. The AMRH initiative is also implemented in the Economic Community of West African States (ECOWAS), Intergovernmental Authority on Development (IGAD) and Economic Community of Central African States (ECCAS). The initiative, which covers more than 85% of countries in Sub-Saharan Africa, serves as a foundation for the establishment of the African Medicines Agency (AMA) [15,29,33].

Under the AMRH Initiative, the AU Model Law on Medical Products Regulation was adopted in 2016 to address the problem of non-coherent medicines laws, ensure effective regulation and promote harmonization [15, 27]. The Model Law advocates for establishment of autonomous agencies with powers to make independent regulatory decisions and to collect

and utilize fees for regulatory services and has been domesticated by more than 12 AU Member States [19,29]. In addition, eleven (11) regional centers of regulatory excellence have been designated since 2014 to provide coordinated and structured regulatory science training through existing academic institutions in partnership with regulatory agencies to ensure sustainable production of regulatory workforce in Africa [19].

Existing regulatory networks have been aligned and integrated into the AMRH governance structure to ensure coordinated interventions and collective impact [19,22-28]. Initiatives such as the African Vaccines Regulatory Forum (AVAREF) coordinated by the World Health Organization (WHO) have played a key role in strengthening vaccines and medicines clinical trials regulation and ethics review capacity on the continent and have been aligned with the AMRH Initiative [19,24,25]. A Network of Official Medicines Quality Control Laboratories for SSA (NOMCOL-SSA) which was initially coordinated by the United States Pharmacopoeia (USP) is another regulatory network which has been integrated into the AMRH governance structure now known as the African Medicines Quality Forum (AMQF) technical committee [19,26–28].

Regional and continental technical committees and Steering Committees have been established to provide technical and strategic oversight respectively while the African Medicines Regulators Conference (AMRC) serves as the Assembly [19]. The AMRH Partnership Platform has also been established as part of the AMRH governance framework to provide the needed technical, financial and political advocacy support [19]. The AUDA-NEPAD and the WHO serve as Joint Secretariat for the AMRH Initiative and in collaboration with the African Union Commission (AUC), they support the AMRC Assembly. **Figure 1.1** below describes the AMRH governance structure.

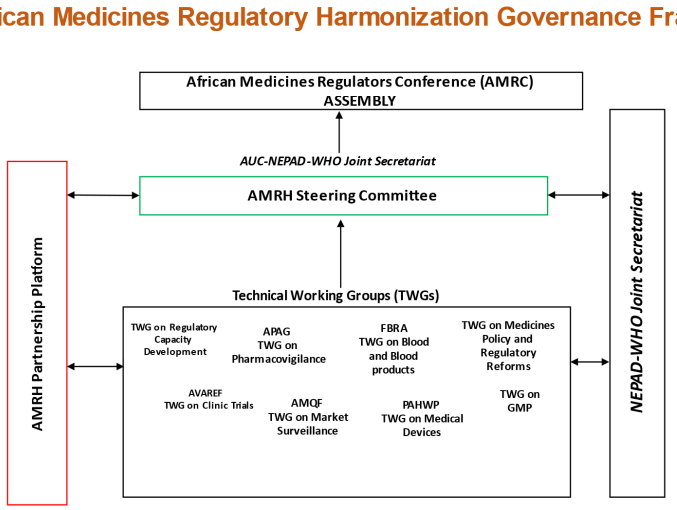

Figure 1.1 The African Medicines Regulatory Harmonization Initiative Governance Structure

Source: African Union Development Agency (AUDA-NEPAD); 2018

Other initiatives such as the WHO Prequalification programme (WHO-PQ) have over the years provided hands-on training for assessors and inspectors of low- or middle-income countries to build their capacity [21]. The WHO-PQ programme has assisted in NMRAs capacity building through their participation in assessment of finished pharmaceutical products (FPPs) and active pharmaceutical ingredients (APIs) and collaborative procedure for accelerated registration of medical products [21]. All these initiatives aim to accelerate the development of new or improved medical interventions for poverty-related neglected diseases (PRNDs); and contribute towards attainment of UHC, the African Union Agenda 2063 and the global 2030 sustainable development goals (SDGs) [15,18,19, 23].

Understanding the relevance of various regulatory interventions implemented at country, regional and continental levels is important for informing regulatory policy reforms undertaken by the AU, governments, and partners [15,22,23,33]. It is for this reason that a study to evaluate the effect of medicines regulatory harmonization initiative in the East

African Community region was undertaken to provide insights on whether or not it is making an impact on national regulatory capacity.

The study aimed to determine factors which have attributed in improving regulatory capacity in the EAC NMRAs. Specifically, the study focused on the level at which countries have i) implemented agreed common technical document (CTD) for registration of medicines in the EAC Partner States ii) implemented common information management systems for medicines registration in each of the EAC Partner States' NMRAs, and whether or not the country's information management system (IMS) is linked in all Partner States and EAC Secretariat. iii) implemented quality management systems (QMS) in each of the EAC Partner States' NMRAs. iv) the level of capacity attained at regional and national levels to implement medicines registration harmonization in the EAC region. v) whether or not a framework for mutual recognition procedure has been developed and implemented in the East African Community Partner States, and lastly vi) whether or not a platform for information sharing with key stakeholders at national and regional level has been established. The research hypothesis is that the EAC MRH Project implemented under the AMRH Initiative has increased regulatory capacity in the EAC Partner States.

The outcome of this study will help governments to objectively assess performance of NMRAs and their participation in regional initiatives. With regular monitoring and evaluation, policymakers will understand what the money invested is producing; whether plans are being followed; the difference being made, and how to strengthen medicines regulatory systems and harmonization initiatives [34].

1.3 THE EAST AFRICAN COMMUNITY (EAC)

The EAC is an intergovernmental organisation composed of six (6) Partner States namely Republic of Burundi, Republic of Kenya, Republic of Rwanda, Republic of South Sudan, the United Republic of Tanzania and Republic of Uganda, headquartered in Arusha, Tanzania (**Figure 1.2).** Covering an area of approximately 2.44 million square kilometres, the six countries have a combined gross domestic product of $ 41.2 billion and an estimated population of over 169.5 million people who share a common history, language, culture and

infrastructure. The EAC would be the ninth-largest population in the world if considered as a single entity [35]. The region therefore provides a unique framework for regional co-operation and integration in political, economic, social and cultural areas including health and pharmaceuticals as exemplified in Chapter 21 (Article 118) of the EAC treaty [36,37].

The EAC aspires to be a prosperous, competitive, secure, stable and politically united region through widening and deepening economic, political, social and cultural integration to improve the quality of life of the people [36,37]. Increasing competitiveness, value-added production, trade and investment is the EAC regional focus [36,37]. The operationalization of the EAC Customs Union and the Common Market have enhanced trade and significantly increased foreign direct investment in the region [36]. In addition, free movement of goods, people, labour, services and capital from one Partner State to another as well as the rights of establishment and residence without restrictionshas been enhanced [36]. In the area of health, the EAC has undertaken joint action towards the prevention and control of communicable and non-communicable diseases to control pandemics and epidemics of communicable and vector-borne diseases [36].



Figure 1.2: The East African Community Map

Source: https://www.google.com/ https://www.kfw-entwicklungsbank.de/International-financing/KfW-Development-Bank/Local-presence/Subsahara-Africa/East-African-Community/

The EAC is one of the regional economic communities (RECs) recognised by the African Union in addition to the other seven. The work of the EAC is structured into seven main Organs namely, the Summit, the Council of Ministers, the Co-ordinating Committee, Sectoral Committees; the East African Court of Justice; the East African Legislative Assembly, and the Secretariat [37]. Its operations are guided by a Treaty which established the Community in 2000 [37]. The Summit comprising of Heads of Government of Partner States gives strategic direction towards the realisation of the goal and objectives of the Community. The Council of Ministers (or simply, the Council) is the central decision-making and governing Organ of the EAC. Its membership constitutes Ministers or Cabinet Secretaries from the Partner States whose dockets are responsible for regional co-operation. Regulations, directives and decisions taken or given by the Council are binding to the Partner States and to all other Organs and Institutions of the Community other than the Summit, the Court and the Assembly. The Secretariat is the executive Organ of the Community which is responsible

for ensuring that regulations and directives adopted by the Council are properly implemented. It comprises the Secretary-General, 4 Deputy Secretaries-General, the Counsel to the Community and hundreds of EAC staff members who carry out the day-to-day work of the EAC as mandated by the Council. The Secretary-General is the principal executive and accounting officer of the Community, the head of the Secretariat and the Secretary of the Summit [37].

1.4 THE EAST AFRICAN COMMUNITY MEDICINES REGULATORY HARMONIZATION (EAC MRH) PROJECT

The East African Community Medicines Regulatory Harmonization Project (EAC MRH Project) was launched in 2012 as part of the AMRH initiative, with a view to have a harmonized and functioning medicines registration system which meets national and internationally recognized standards [38]. At the inception of the MRH Project, five Partner States with six NMRAs were involved namely; Republic of Burundi (Unit in the Ministry of Health), Republic of Kenya (Pharmacy and Poisons Board), Republic of Rwanda (Unit in the Ministry of Health), the United Republic of Tanzania with two NMRAs (Tanzania Medicines and Medical Devices Authority for Mainland and Zanzibar Food and Drugs Board for Island), and Republic of Uganda (National Drug Authority) [39]. Since South Sudan had not acceded to the Treaty establishing the EAC, their NMRA was not included in this study.

A baseline survey conducted in 2010/11 in the EAC NMRAs showed marked variation in regulatory capacity among participating Partner States and the EAC Secretariat in terms of both numbers and skills [39,40]. Infrastructure varied in all the Partner States and required expansion to cater for the full functions of medicines regulation. Rwanda, Burundi and Zanzibar had limited physical infrastructure to carry out the full range of medicines regulatory activities. All of the six NMRA's had different requirements for application for registration of pharmaceutical products, both in terms of format and content. The guidelines were not comprehensive to cover all the key regulatory requirements hence jeopardizing the harmonization process. There was no mechanism for sharing regulatory information among the NMRAs [39].

The study showed that all the EAC Partner States had different legal frameworks for regulation of pharmaceuticals with the scope of regulated products varying from country to country. In Tanzania, Kenya and Uganda the laws provided for the establishment of NMRAs as semi- or autonomous agencies, whereas for Burundi and Rwanda regulatory functions were administered by the respective Ministries of Health, and in Tanzania [38]. Tanzania Medicines and Medical Devices Authority (TMDA) for Tanzania Mainland operated as a semi-autonomous body while in Zanzibar, although the law provided for semi-autonomy, operationally the Zanzibar Food and Drugs Board (ZFDB) was still operating as a department under the Ministry of Health. Similarly, the Pharmacy and Poisons Board (PPB) of Kenya, was headed by the Registrar who also served as a Chief Pharmacist in the Ministry of Health. The National Drug Authority (NDA) of Uganda operated as a fully autonomous body.

The survey also showed that TMDA, PPB and NDA charge fees for regulatory work and receive little or no government subvention. On the other hand, in Zanzibar, Rwanda and Burundi, their governments fully funded the regulatory work. In all the countries, lack of human resources to perform core regulatory functions was the main constraint, especially so for biological products, herbal medicines and medical devices. Only the TMDA was ISO 9001:2000 certified before the EAC MRH Project was launched [38].

During the baseline study, marketing authorization (MA) was issued in all the Partner States NMRAs with the exception of Rwanda and Burundi. ZFDB recognized MAs issued by TMDA but also had legal provisions and arrangements to independently issue its own [38]. Only TMDA had a functioning quality management system (QMS). Data requirements for marketing authorization were well elaborated by TMDA and NDA; however, the latter had no written procedures for the assessment of applications. TMDA, on the other hand had standard operating procedures including one for fast-tracking of medicines evaluation and registrations used in the case of priority diseases and orphan drugs. In as far as regulatory inspections are concerned all countries except Rwanda and Burundi performed inspection of manufacturing facilities. **Table 1.1** below summarises findings of the baseline survey of NMRAs in the EAC region.

Table 1.1: EAC Situation Analysis: Summary of Key Findings; 2010/11

	Tanzania (Mainland)	Tanzania (Zanzibar)	Rwanda	Burundi	Kenya	Uganda
1 National regulatory system						
1.1. The legislation provides for the establishment of an NRA and clearly defines its mission, terms of reference, jurisdiction, roles and responsibilities.	Yes	Yes	No	No	Yes	Yes
61.2 The NRA has the authority and mechanisms to collect fees and use the funds generated internally.	Yes	Yes	No	No	Yes	Yes
1.3 The NRA has implemented a quality management system (QMS) for all regulatory procedures.	Yes	No	No	No	No	No
2 Marketing authorization						
2.1 The legislation requires holding a marketing authorization (MA) before putting a pharmaceutical product on the market.	Yes	Yes	Yes	Yes	Yes	Yes
2.2 The Regulatory authority issues a marketing authorization (MA) before putting a pharmaceutical product on the market.	Yes	Yes	No	No	Yes	Yes
2.3 There are procedures followed for issuance of marketing authorization (MA).	Yes	Yes	No	No	Yes	Yes
2.4 A written fast-track mechanism is followed for medicines used in priority diseases & orphan drugs	Yes	No	No	No	No	No
2.5 There is a legal requirement specifying the length of time for which the MA is valid and defining when MAs should be renewed.	Yes	Yes	Yes	No	Yes	No
3 Licensing of manufacturers						
3.1 A practical guidance document is available with detailed information on compliance with good manufacturing practice	Yes	No	No	No	Yes	Yes

(GMP) requirements.						
3.4 Defined timelines and tracking mechanisms are set for the assessment of applications.	Yes	No	No	No	No	No
3.5 The list/database of all licenses is publicly available.	Yes	Yes	No	No	Yes	Yes
4 Regulatory inspections						
4.1 Premises where regulated activities are performed are inspected in order to check compliance with regulatory requirements	Yes	Yes	No	No	Yes	Yes
4.2 Possession of a license is a requirement for manufacturing, wholesale, retail and export of pharmaceuticals	Yes	Yes	Yes	Yes	Yes	Yes

Source: EAC Situation Analysis Report, 2010/11

The outcome of the survey resulted in the categorization of countries into two groups. Those with some level of capacity namely Kenya, Tanzania (Mainland) and Uganda and those with limited capacity i.e. Burundi, Rwanda and Tanzania (Zanzibar) [38]. The report informed the development of a project proposal to harmonize medicines regulatory systems in the EAC region which was launched in 2012. Under this project, a Steering Committee was established to provide strategic oversight on project implementation, composed of Heads of NMRAs and Chief Pharmacists of respective Partner States in the region and AMRH Partners. In addition, expert working groups (EWG's) on medicines evaluation and registration, good manufacturing practice (GMP), quality management systems (QMS) and information management systems (IMS) were established to provide technical guidance. The structure of the EAC MRH Project is indicated in **Figure 1.3** below.

The AMRH Partners including the African Union Development Agency – New Partnership for Africa's Development (AUDA-NEPAD); NMRAs; Swissmedic, WHO, World Bank, Bill and Melinda Gates Foundation (BMGF), Swiss Agency for Therapeutic Products; UK Department for International Development (DFID) and other partners provided the needed technical, financial, and political advocacy support. A multi-donor trust fund was established at the World Bank to support the AMRH initiatitve with an initial injection of $12.5 million from

BMGF and $3million from DFID. $5.5 million was allocated to the EAC MRH Project for the first phase 2012-2015.

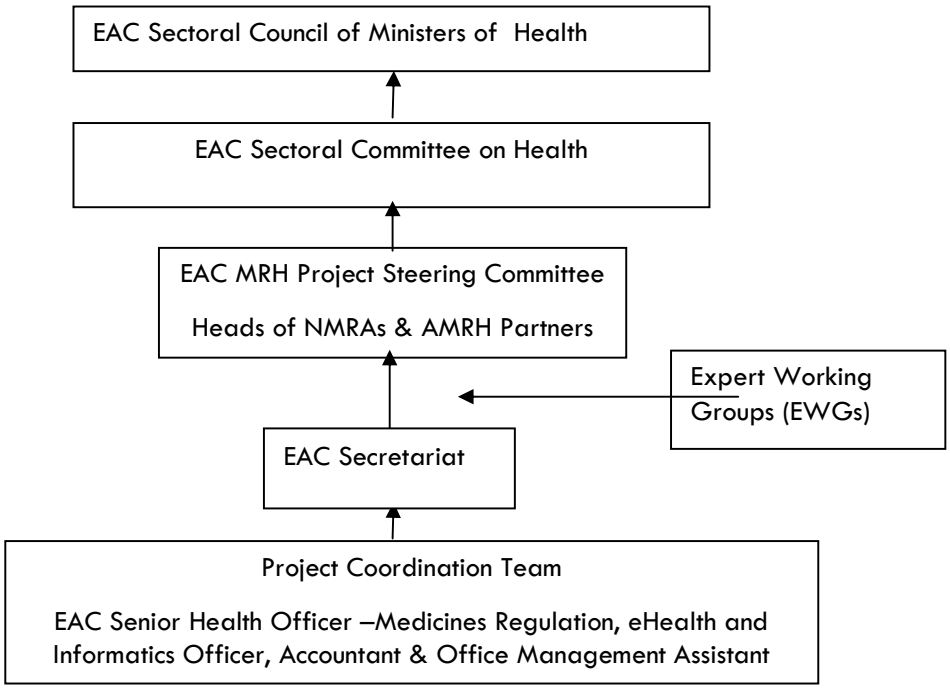

Figure 1.3: Structure of the EAC MRH Project Management

1.5 PROBLEM STATEMENT

A baseline survey of NMRAs in the EAC region in 2010/11 identified gaps in regulatory systems across countries [39], which formed the basis for the EAC MRH project proposal and eventual launch in 2012. Regional harmonization of regulatory requirements and collaboration among NMRAs is considered as one of the ways to address regulatory capacity challenges [41]. Limited capacity and weak regulatory systems have attributed to circulation of falsified and substandard (SF) medical products particularly in low- and middle-income countries (LMICs) hence posing a public health risk [41]. Sharing of regulatory information, as well as resources and knowledge, are critical factors for increasing regulatory capacity [42]. Regulatory harmonization and cooperation among NMRAs assist in harmonizing regulatory requirements and standards, minimizing duplication of efforts, facilitating joint

assessment of dossiers and inspection of manufacturing sites hence building confidence and capacity with subsequent reduction of the time it takes to place a product in a particular market [42]. This research will document best practices to facilitate decision making by policymakers and guide regulation of medical products across countries, regions continents and the globe.

1.6 AIMS

According to WHO, for a country to have the capacity to regulate medical products it requires; i) a comprehensive legal basis (legislation and regulations) and technical guidance (guidelines, norms, standards, specifications and procedures) to guide the industry; ii) a national medicines regulatory agency that coordinates and oversees the regulatory system; iii) an adequate number of qualified and skilled professionals competent to design and/or implement sound technical and scientific tools and legal provisions; iv) adequate and sustainable funding mechanisms; and v) ability to carry out monitoring and evaluation [13].

The study aims to determine factors which have attributed to EAC MRH Project success and the extent to which the EAC MRH Project has contributed to improve regulatory capacity. The outcome of this research will serve as a useful guidance for monitoring and evaluation of regional medical products regulatory harmonization initiatives and/or networks in Africa and across the globe.

1.7 RESEARCH OBJECTIVES

The objectives of this study are to: i) evaluate the effect of the MRH Project on the regulatory capacity of the EAC Partner States NMRAS, four years after its implementation; and ii) provide evidence-based information for policy and decision making.

Specifically, the study focused on the level at which countries have; i) implemented an agreed common technical document (CTD) for registration of medicines in the EAC Partner States; ii) implemented common information management systems for medicines registration in each of the EAC Partner States' NMRAs, and whether or not the country information management system (IMS) is linked between all Partner States and integrated to the EAC

Secretariat; iii) implemented quality management systems (QMS) in each of the EAC Partner States' NMRAs; iv) the level of capacity attained at regional and national levels to implement medicines registration harmonization in the EAC region; v) whether or not a framework for mutual recognition procedure has been developed and implemented in the East African Community Partner States; and lastly vi) whether or not a platform for information sharing with key stakeholders at national and regional level has been established.

1.8 RESEARCH HYPOTHESIS

Before launch of the EAC MRH project in 2012, a baseline survey conducted in 2010/11 identified several gaps in the national medicines regulatory systems in the 6 NMRAs. Interventions developed as part of the MRH Project aimed at addressing identified gaps [39]. The research hypothesis is that the EAC MRH Project implemented under the AMRH Initiative has increased regulatory capacity in the EAC Partner States.

CHAPTER 2: STUDY DESIGN AND METHODOLOGY

2.1 INTRODUCTION

This chapter comprises 5 sections including introduction. The 2nd section provides explanation on the study design and sampling, the 3rd section is on the indicators' development and measurement, and the 4th focuses on documentary review and data sources. Other sections are as follows; data analysis – section 5, description on studied parameters – section 6, and ethics approval – section 7.

2.2 THE STUDY DESIGN AND SAMPLING

An exploratory, mixed method design using both qualitative and quantitative data was employed in this study. Data was collected from all the six NMRAs in the EAC Partner States namely, the Republics of Burundi Kenya, Rwanda, Uganda, and the United Republic of Tanzania (with two NMRAs). Data from the six NMRAs was collected through a combination of semi-structured interviews, questionnaires, and checklists.

Due to the similarity of the target population on all the important variables of the study, a purposive sampling was used in selecting the informants. Participation in medicines policy and regulation of medical products in a country and regional level was used as inclusion criteria.

Annual data collection was conducted during the 2010/11-2014/15 period whereas for some indicators, a three yearly data collection was done during the 2010/11– 2015/16 period. In each case, data from the starting year served as baseline. The questionnaire and checklist was developed based on the information obtained from the preliminary situational analysis study [30]. Moreover, additional questions were adopted from the WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems [31]. Validation of the data collection tools was conducted by piloting them with some of the prospective respondents in all studied NMRAs.

During the pilot phase, the Head and one monitoring and evaluation expert in each NMRA, as well as the project officer of the EAC MRH project responded to self-administered questionnaires and checklists (**Annexes 7.1-7.2),** A total of 13 respondents were selected based on their roles and involvement in medicines policies and regulatory activities. Based on feedback from respondents, the tools were refined to accommodate aspects related to NMRAs involvement in regional joint review of dossier applications and GMP inspections.

The second round involved semi-structured face-to-face interviews with one staff each from medicines registration, GMP inspections, legal affairs, human resource, and finance departments in addition to the previous set of respondents. One to two respondents were involved in 1 to 2 hours long interview session each. An invitation letter and interview topic guide were sent to the interviewees in advance. A permission to record the responses in a written form was obtained from all respondents. Confidentiality of all respondents was observed. Interviews were conducted on a face-to-face basis, with each session lasting for 1 to 2 hours. Oral responses were recorded by means of selective written notes, which were thereafter subjected to qualitative analysis while quantitative data was collected using an excel sheet. Follow up visits were conducted aiming at collecting the missing data and validating the previously collected data.

2.3 INDICATORS DEVELOPMENT AND MEASUREMENT

While the WHO-GBT indicators provide for evaluation of regulatory systems at a national level, there are no tools for measuring the performance of regional medicines regulatory harmonization initiatives and/or networks hence the need for developing these indicators. In addition, indicators developed by the Centre for Innovation in Regulatory Science (CIRS) Programme on Optimizing Efficiency in Regulatory Agencies (OpERA) provided useful information on regulatory review process undertaken by NMRAs.

Some indicators on national regulatory systems and registration and marketing authorization (MA) including elements on availability of national medicines policy and law establishing the NMRA, and legal provisions, regulations, and guidelines for registration and/or MA were

drawn from the WHO-GBT. In addition, availability of human resources to perform registration and MA activities, and the existence of an advisory or scientific committee were also captured from the WHO-GBT indicators.

Indicators which were modified from WHO-GBT to address the need for assessing the regional regulatory framework include, the existence of a system at national and regional level to monitor timelines for the assessment of the applications, legal provisions, regulations and requirements for transparency and dissemination of information to the public and relevant stakeholders, the level of implementation of EAC QMS and attainment of ISO Certification by the NMRA. Others are NMRAs participation in regional, IMS and transparency. NMRA financing, NMRA governance, partnership and coordination and mutual recognition indicators are another modification to the WHO-GBT. On the other hand, the CIRS OpERA programme indicators which focus on optimising performance of regulatory review process to help regulators integrate a practice of tracking and measuring regulatory performances within their agencies was also imbedded in the indicators. The WHO-GBT benchmarking reports and the OpERA are also used as source of data as indicated in Table 2.1

Based on this, a set of 29 indicators were developed and grouped in 9 main categories to ensure objective assessment of the EAC MRH project. Each indicator was further refined to facilitate users' understanding and to ensure accuracy of data collected. The indicators were further classified into various types; input, output, outcome and impact indicators. Two workshops were held in May 2016 and November 2017 involving monitoring and evaluation focal points from the EAC NMRAs, RECs and WHO to validate data collected and the indicators tool.

Policy and legal framework: Two indicators were used for assessment. The first is the availability, comprehensiveness, and how recently the national medicines policy was reviewed. According to the guidance document, the current policy means that which was reviewed in the past 5 years. The second indicator assessed the availability, the year of enactment and the comprehensiveness of a national medicines law. The AU Model Law on

Medical Products Regulation was used as a benchmark for comprehensiveness of the national law [29].

NMRA governance: This was assessed using two indicators. NMRA autonomy looked at three categories, fully autonomous agency, semi-autonomous agency, or a department under the Ministry of Health. According to the WHO, an autonomous agency means a financially and operationally independent body from other government bodies but accountable to the public [43].

NMRA financing: According to the guidance document, the level of funding was measured by assessing the total annual funding for NMRA (in USD) as a proportion for the population each year. However, due to limitations in data collected, five indicators namely policy on NMRAs funding; the level of autonomy; reliability of funding (annual budgets against actual funding); sources of revenue; and expenditure patterns were used for measurement. The reliability of funding was used to determine the ability of the NMRA to sustain its activities using revenue generated from various sources including government.

Medicine registration and good manufacturing practice (GMP) systems: Indicators for this component measured the existence of a legal framework for registration and GMP inspection; a mechanism for receiving applications, evaluating dossiers and providing marketing authorization for medicines; existence of staff, use of regional harmonization guidelines, participation and uptake of the outcome of regional review and inspection processes.

Functional QMS: The first indicator assesses the level of implementation of EAC QMS Guidelines by NMRAs based on ISO 9001:2015 as means to facilitate the delivery of quality regulatory services to customers. The second indicator measures the actual ISO certification as an indication of management commitment to quality service delivery, in this case focusing on registration and GMP inspection systems. The third indicator measures availability of mechanism to address customer concerns.

IMS: was measured by assessing the level of implementation of EAC Integrated IMS requirements and guidelines.

NMRA human resource capacity: two indicators for measurement include medical products regulatory experts' density and internal NMRA capacity. The former was to be measured by the number of evaluation and registration experts (assessors) as a proportion of applications received per year and the number of GMP inspectors per GMP inspections conducted per year. The internal NMRA capacity was to be measured by the percentage of external expertise used in the NMRA per regulatory function. However, the lack of data made this measurement difficult. Instead, the assessment was based on data provided on 14 sub-indicators.

Level of transparency: looks at the availability of key regulatory information to the general public and mechanisms of engaging stakeholders using different platforms.

Partnerships and coordination: two indicators for assessment include the number of partners that are coordinated under the EAC MRH Project; and the proportion of partners supporting regulatory systems strengthening in alignment with the AMRH framework.

Table 2.1 is a matrix which provides the indicator title, purpose, rationale for selecting the indicators, method of measurement, measurement frequency and unit of measurement. It also provides the reporting level, frequency of reporting and data source whether generated from the WHO NMRA GBT, RECs, Government Gazette, Ministry of Health, Ministry of Justice, or CIRS OpERA programme, just to mention a few. **Annex 7.3.** is the guidance notes for data collection which indicate the data sources, indicator classification, data type and institution responsible for reporting on the respective indicators. Also included in the guidance document is data collected annually on NMRA financing; registration and GMP inspection systems and NMRA human resource capacity; QMS as well as partnership and coordination. Data on availability and comprehensiveness of policy and legal frameworks, NMRA governance, IMS, communication and publication of regulatory policies, regulations and guidelines as well as stakeholders' engagement was collected on a three-yearly basis i.e. 2010, 2013 and 2015/16.

It is intended that lessons learnt from this research be used as a way of refining the indicators matrix and guidance document for further use in the monitoring and evaluation of similar projects in other RECs.

Table 2.1: Indicators Matrix

NO.	INDICATOR TITLE	TYPE	REPORTING LEVEL	FREQUENCY	DATA SOURCES
CATEGORY 1:	**POLICY AND LEGAL FRAMEWORK**				
Indicator 1:	National Medicines Policy (NMP)	Input	NMRA	Three yearly	WHO NMRA GBT, Government gazette, Ministry of Health
Indicator 2:	Legal framework governing the regulation of medical products	Input	NMRA	Three yearly	WHO NMRA GBT, Government Gazette, National Law, Ministry of Justice library, NMRA records
CATEGORY 2:	**NMRA GOVERNANCE**				
Indicator 3:	NMRA level of autonomy	Output	NMRA	Three yearly	WHO NMRA GBT, CIRS OpERA programme, Government gazette, NMRA Financial report, Governance structure
Indicator 4:	Availability of structures to support NMRA decision-making process	Process	NMRA	Three yearly	NMRA Organisation/governance structure, Medicines law
CATEGORY 3:	**NMRA FINANCING**				
Indicator 5:	Level of NMRA funding	Input	NMRA	Annually	CIRS OpERA programme, NMRA records, Ministry of Health
Indicator 6:	Reliability of NMRA funding	Input	NMRA	Annually	CIRS OpERA programme, Central Medical Stores records, Ministry of finance records, Approved annual national budget, NMRA records
CATEGORY 4:	**MEDICINES EVALUATION AND REGISTRATION, AND GOOD MANUFACTURING PRACTICE (GMP) INSPECTION SYSTEMS**				
Indicator 7:	Availability of guidance and procedures for registration of medicines	Process	NMRA	Annually	WHO NMRA GBT, CIRS OpERA programme, NMRA records, Government policies and legislation
Indicator 8:	Availability of a Good Manufacturing Practice (GMP) inspection guidance and procedure	Process	NMRA	Annually	WHO NMRA GBT, NMRA records, Government policies and legislation, WHO Assessment Reports
Indicator 9:	Availability of a process to track product registration applications and timelines	Process	NMRA	Annually	WHO NMRA GBT, CIRS OpERA programme, NMRA records
Indicator 10:	Existence of a regional policy stimulating review timelines	Outcome	Regional	Annually	CIRS OpERA programme, NMRA records
Indicator 11:	Number of products applications with registration decisions per annum	Outcome	Regional	Annually	CIRS OpERA programme, NMRA records
Indicator 12:	Proportion of NMRAs participating in joint assessments	Output	Regional	Annually	CIRS OpERA programme, REC records
Indicator 13:	Proportion of product applications jointly assessed/ reviewed at regional level	Outcome	Regional; continental	Annually	CIRS OpERA programme, REC records
Indicator 14:	Proportion of NMRAs who made decisions within standard time based on regional reports/ assessment/s	Outcome	Regional	Annually	CIRS OpERA programme, NMRA records
Indicator 15:	Proportion of decisions made at country level based on regional report for which a decision was made within standard time	Outcome	Regional	Annually	CIRS OpERA programme, NMRA records
Indicator 16:	Proportion of NMRAs using regionally harmonized guidelines for product registration	Output	Regional	Annually	CIRS OpERA programme, NMRA Records; REC Records
Indicator 17:	Proportion of NMRAs using regionally agreed systems and processes (Joint assessment)	Output	Regional	Annually	CIRS OpERA programme, NMRA; REC Records
Indicator 18:	Joint Good Manufacturing Practice (GMP) inspections conducted regionally	Output	Regional	Annually	REC records
Indicator 19:	Percentage of Good Manufacturing Practice (GMP) inspection decisions made based on document review	Output	Regional	Annually	REC records
CATEGORY 5:	**FUNCTIONAL QUALITY MANAGEMENT SYSTEMS (QMS)**				
Indicator 20:	Implementation of Quality Management System (QMS) requirements by NMRA	Process	NMRA; regional	Annually	CIRS OpERA programme, NMRA QMS Records
Indicator 21:	Percentage of NMRAs ISO 9001: 2015 Certification	Output	NMRA; regional	Annually	NMRAs QMS Records
Indicator 22:	Availability of mechanism for addressing customer concern	Process	NMRA; regional	Annually	WHO NMRA GBT, NMRAs, Customer Complaint Reports, Customer Satisfaction Surveys/Index
CATEGORY 6:	**INFORMATION MANAGEMENT SYSTEMS (IMS)**				
Indicator 23:	Implementation of requirements for an integrated IMS	Output	NMRA; regional	Annually	WHO NMRA GBT, NMRA IMS
CATEGORY 7:	**LEVEL OF TRANSPARENCY**				
Indicator 24:	Availability of key regulatory information to the general public using different platforms	Output	NMRA; regional	Three yearly	WHO NMRA GBT, NMRAs Website, Government Gazette; WHO reports
Indicator 25:	Engagement of stakeholders on different platform(s)	Process	NMRA; regional	Three yearly	NMRA Records, REC Records, NEPAD Agency records
CATEGORY 8:	**NMRA HUMAN RESOURCE CAPACITY**				
Indicator 26:	Medical products regulatory experts 'density	Input	NMRA	Annually	CIRS OpERA programme, NMRA records
Indicator 27:	Internal NMRA capacity	Input	NMRA	Annually	CIRS OpERA programme, NMRA records
CATEGORY 9:	**PARTNERSHIPS AND COORDINATION**				
Indicator 28:	Partnership coordination towards collective impact on regulatory systems strengthening	Process	NMRA; regional	Annually	Mutual recognition agreements, MOUs, Requests sent to/received from partners, National partnership agreements
Indicator 29:	Proportion of partners that are aligning to the AMRH framework	Input	NMRA; regional	Annually	Income statement of the NMRA, MOUs, Mutual recognition agreements

2.4 DOCUMENTARY REVIEW AND DATA SOURCES

Three phases of document review were conducted. The first was to review the status of medicines regulation on the African continent based on original research, published reports and data from various organizations [15]. This provided an overarching account of NMRAs status in Africa and existing opportunities to strengthen their regulatory systems and harmonization efforts across the continent.

In the second phase of document review, the African Medicines Regulatory Harmonization (AMRH) initiative was reviewed with a view to providing information on various regional medicines regulatory harmonization, collaborations and networks among countries as basis for further in-depth analysis of the East African Community (EAC) medicines regulatory harmonization (MRH) project [19].

The third phase entailed a review of relevant documents on the EAC MRH project including the report of situation analysis study on national regulatory systems conducted by the EAC in 2010/11 which was used as a baseline [39]. Other reports and publications were also used as source of information including reference to official websites of the NMRAs in the EAC region. Information on prevailing medicines policies, laws, regulation, technical guidelines, and procedures were reviewed to provide insight on existing data on regulation of medical products in the EAC region.

A review of relevant documents was done to understand the meaning of data generated hitherto. Secondary data from various study reports as well as other international publications and workshop deliberations were used as a reference to determine whether information generated addressed issues relevant to the research.

2.5 DATA ANALYSIS AND DESCRIPTION OF STUDIED PARAMETERS

2.5.1 Data Analysis

Qualitative data analysis and interpretation was carried out on indicators relating to availability of the national medicines policies, laws, guidelines, provisions, legal

frameworks, level of autonomy, regulatory standards, guidance, and procedures as well as status of implementation of different modules. Qualitative data obtained using questionnaires, interviews and desk reviews of documents was organized, analysed, and evaluated manually with the help of tables on MS Excel®.

Arithmetic means and standard deviations were determined for all numerical data across all years for each individual respondent NMRA. Observations were also made on the presence of any trend in the course of time from the baseline to the end of the study duration. Where only a single point data was provided by the respondents, it was reported as such. Due to lack of data from some agencies, only the available data set was used in statistical analysis and interpretation.

Categorical (Non-numerical) data were reported and analysed as Yes or No, with the specific year of their first appearance being noted and indicated in the parenthesis in the tables of results. For financial reports, the prevailing average annual USD currency exchange rate for each country was used for analysis. The average annual exchange rates of Tanzanian, Kenyan, Ugandan, Rwandese and Burundian currencies against the USD ranged as TZS (1585.3 – 2188.2), KES (84.2 – 101.5), UGX (2349.4 – 3369.4), RWF (579.9 – 783.1) and BIF (1159.7 – 1657.6) respectively over the studied period [44].

Quantitative data were analysed for means and standard deviation using Microsoft Excel©, whereas document analysis was used to extract organize and interpret data from policies and laws. All data were finally summarized using tabulation of the identified indicators against each of the NMRAs, arranged in a side-by-side order for easy comparison and comprehension. Evaluations were made on the consistency and trends of each indicator across the NMRAs and years under study.

2.5.2 Description of the studied parameters

The survey was intended to explore in a quantitative and qualitative manner the following parameters, regulatory capacity, efficiency, transparency, sustainability, and the level of coordination of regulatory interventions.

Regulatory capacity: This is defined as a combination of various parameters including the availability of a comprehensive legal framework for regulation of medical products, availability of regulations and technical guidance to guide the industry; existence of an NMRA that coordinates and oversees the regulatory system in a country; adequate number of qualified and skilled professionals competent to design and/or implement sound technical and scientific tools and regulations; adequate and sustainable funding mechanisms; and ability to carry out monitoring and evaluation.

Efficiency: Determines the time taken to achieve the intended goal within reasonable time, effort and cost, in this case it is the approval of products within a specified standard time.

Transparency: This parameter looks at availability to the public of information such as laws, regulations, guidelines, alerts and any relevant regulatory information including the summary basis for approval of products.

Sustainability: Looks at the ability and reliability of financing regulatory activities by the NMRA and availability of the human resource capacity (both in number and qualification) to perform assigned duties.

Level of coordination of regulatory interventions: Is defined as the ability to identify the type and number of partners providing technical, financial and/or political support and the existence of mechanisms for coordination.

Technical cooperation and mutual recognition: These assess harmonization of technical guidelines and procedures among countries, collaboration through joint review of dossiers and inspection of manufacturing sites, exchange of regulatory information and recognition of each other's regulatory decisions.

2.6 ETHICS APPROVAL

Ethics approval was granted by the WITS Human Research Ethics Committee on 31st July 2015 through clearance certificate No. M150751. In addition, national ethical clearances were granted by the respective national research ethics committee as indicated in **Annex 7.4.**

CHAPTER 3: RESULTS

3.1 INTRODUCTION

In this Chapter, results are presented in a way that as much as possible trends on the performance indicators are analyzed over the study period. They are reported in the following categories, policy and legal frameworks – Section 2, regulatory governance – Section 3, NMRA financing – Section 4, medicines registration and inspection systems – Section 5, functional information management systems – Section 6, functional quality management systems – Section 7, partnerships and coordination – Section 8, transparency and accountability – Section 9, and a framework for mutual recognition – Section 10.

3.2 POLICY AND LEGAL FRAMEWORK

The national medicines policy (NMP) is a framework for the coordination of pharmaceutical sector activities involving all the main actors including mechanisms that will ensure effective regulation and quality assurance of medicines in a country. It is an overarching government commitment to a goal and guidance for action with the overall objectives of ensuring access, quality, and rational use of drugs in a country [45]. This study looked at availability of a NMP, how current it is and whether or not it provides a statement on establishment of an autonomous NMRA with clear vision and mission; as a measure of government commitment in ensuring effective regulation of medical products in a country. According to the indicators guidance, indication of the year of official approval and any approved updates of the NMP by the cabinet within 5 years is a measure of how dynamic the government is in incorporating any new developments and advancements in the sector.

In reviewing the legal framework, the research investigated the availability of a medicines law in a country, the year of enactment and comprehensiveness. According to the indicators' guidance, the year of enactment of the law and coming into force is a measure of political will and commitment by the government. While Laws, Acts or

Statutes are enacted by Parliaments give power to NMRAs to control medicines in their respective territories, regulations on the other hand are prepared under the Act to provide details of how the market is regulated [46]. It is therefore important that Laws which serve as the foundation for regulation, are comprehensive enough covering all areas of pharmaceutical activities, a broad range of medical products and provisions for adequate powers to the NMRA to control and regulate the pharmaceutical market in a country [47].

A total of **nine (9) indicators** were used to evaluate the availability and comprehensiveness of policy and legal frameworks within the NMRAs in the EAC partner states as shown in **Table 3.1.** The NMP was reported to be available in all five states, which were approved by the cabinet Ministers as early as 2007 in Tanzania, the latest being in Rwanda which was approved by the Government in 2016. Other NMPs in the order of their approval include Kenya (2012), Burundi (2012), Zanzibar (2008) and Uganda (2015). It was further indicated that the NMP in each state entailed a provision for the establishment of an autonomous NMRA. For instance, the NMP of Uganda recognises the importance of regulation and quality assurance and the role of the National Drug Authority (NDA) as a government body responsible for assuring the quality of all medical products in the country [48]. It further underscores the contribution of NDA, regional and continental regulatory harmonization efforts in improving the quality and safety of products circulating in the Ugandan market [48].

While this research shows that the NMP of Kenya was approved by the cabinet in 2012, only the 1994 version is publicly available [49]. The policy provides for regulatory control activities such as drug control and administration, drug registration, scheduling of drugs, pharmaceutical inspectorate, clinical trials, traditional medicines and professional associations and ethics. On quality assurance, the policy provides for the establishment of a national drug quality control laboratory (NDQCL) as a separate body from the Kenya Pharmacy and Poisons Board as the NMRA. In addition, GMP and the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce forms the basis for a national certification scheme for the import and export of pharmaceuticals, as part of the NMP [49].

In Zanzibar, the first NMP was approved by the government in 1991, as part of the overall National Health Policy [50]. The current NMP in Zanzibar recognises the need for an effective and comprehensive law for regulation and control of food, medicines, medical devices, cosmetics, herbal medicine, and poisons, under the Zanzibar Food, Drugs and Cosmetics Act, No, 2, of 2006. The policy also recognises the capacity limitations faced by the Zanzibar Food and Drugs Board (ZFDB) and the need for collaboration with Tanzania Medicines and Medical Devices Authority (TMDA) of Tanzania- Mainland in its effort to regulate the pharmaceutical market in the Island. Furthermore, the policy emphasises the need to strengthen ZFDB capacity in the area of registration of medicines, inspection of premises and imports, laboratory testing and post marketing surveillance of medical products [50].

The current NMP in Tanzania-Mainland which was approved by the government in 2007 is the second edition which precedes the publicly available version of 1991 [7]. The policy emphasises the need for an effective NMRA, quality assurance and quality control mechanisms. Drug registration and drug inspection are considered as important tools for quality assurance of medical products and the need to link NMRA with NDQCL activities.

Unlike the situation in 2009, the approval of the first National Pharmacy Policy of Rwanda in 2016 as an integral part of the National Health Policy is a written expression of the Government of Rwanda's determination and commitment to improving the pharmaceutical sector [51]. It underscores the need to delineate the policy formulation and regulatory functions undertaken by the Pharmacy Department under the Ministry of Health, by establishing the Rwanda Food and Drugs Authority (RFDA) and the National Pharmacy Council (NPC) to regulate medicines, other health commodities and technologies; and pharmacy profession; respectively [51].

All the NMRAs (6/6) also indicated the availability of laws to regulate medicines in their countries reported to be enacted as early as 1957 in Kenya, as amended in 2009. Others include Burundi (1980), Uganda (1993), Tanzania-Mainland (1978 as repealed in 2003, and amended in 2004 and 2014), Tanzania-Zanzibar (1986 as repealed in

2006 and amended in 2016), and in Rwanda having enacted such a law in 2013 [52–57].

The level of autonomy and the scope of products regulated varied among countries in the region. While details of autonomy levels are provided in a separate section, the scope of products is such that TFDA and ZFDB regulate food and cosmetics in addition to medical products. Kenya Pharmacy and Poisons Board, on the other hand, regulates medical products and pharmacy profession under the same law.

This research has shown progress in the review of both NMPs and Medicines Laws by the EAC Partner States as exemplified in **Figure 3.1**. While only three countries (50%) indicated the availability of NMPs during the baseline study, all six now have policies with clear vision and indication for establishment of a semi- or autonomous NMRA. The level of autonomy of NMRAs is also changing. While a Unit under the Ministry of Health was responsible for regulation of medical products in Rwanda, now the Food and Drugs Authority has been established under an Act of parliament of 2013 [54]. The ZFDB has been transformed into a semi-autonomous Agency under the oversight of an Advisory Board while the Executive Director is responsible for day-to-day management of the Agency. Bills for review of medicines laws in Burundi, Kenya and Uganda are at advanced stages of consideration by the national parliaments. The scope of products to be regulated by NMRAs in the EAC region is also being harmonized based on decision by the Council of Ministers to have Food and Drugs Authorities, using the Tanzania Model [58].

In terms of comprehensiveness of medicines laws, two out of six (33%) NMRAs indicated having comprehensive national laws. Benchmarking of the national laws with AU Model Law conducted by the EAC Partner States has shown considerable variation on key provisions that are necessary to ensure effective regulation of medicines [58].

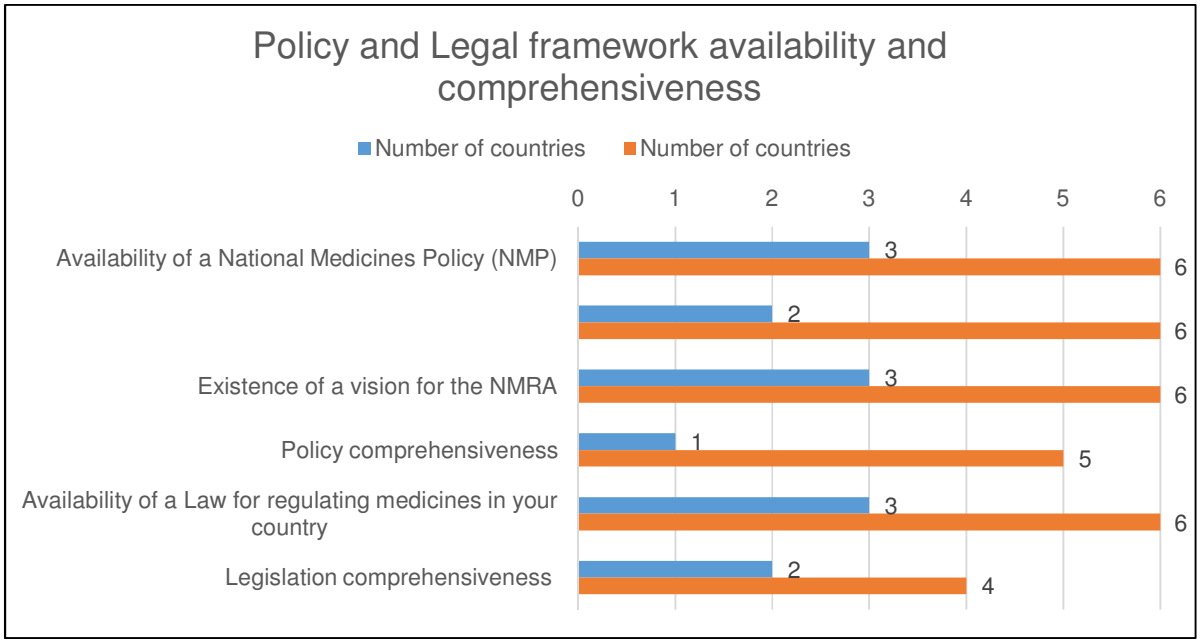

Figure 3.1: The Status of National Medicines Policies and Medicines Laws in the EAC region; 2010/11 – 2015/2016

Table 3. 1 Policy and Legal Frameworks in the EAC Partner States; 2010/11 – 2015/16

	National Medicines Regulatory Agency					
Indicator	**Burundi**	**Kenya**	**Rwanda**	**Tanzania**	**Uganda**	**Zanzibar**
Availability of a National Medicines Policy (NMP)	Yes	Yes	Yes	Yes	Yes	Yes
Year of approval of the NMP by the Cabinet of Ministers	2012	2012	2016*	2007	2015	2014
Availability of a provision in the NMP for establishment of an autonomous national medicines regulatory agency (NMRA)	Yes	Yes	Yes	Yes	Yes	Yes
Existence of a vision for the NMRA	Yes	Yes	Yes	Yes	Yes	Yes
Policy comprehensiveness	Yes	Yes	Yes	Yes	Yes	Yes
Legal framework availability	Yes	Yes	Yes	Yes	Yes	Yes
Availability of a Law for regulating medicines in your country	Yes	Yes	Yes	Yes	Yes	Yes
Year of enactment of medicines law	1980	1957 (as amended in 2009)	2013	1978, (repealed 2003 and amended in 2004 & 2014)	1993	1986 (repealed in 2006 & amended in 2016)
Legislation comprehensiveness	No	No	Yes	Yes	Yes	Yes

*NB: - = No data available/submitted *Secondary data*

Source: Republic of Rwanda National Pharmacy Policy. 2016.

Available: https://www.moh.gov.rw/fileadmin/templates/policies/Pharmacy-Policy_Rwanda-2016.pdf

In addition to policy and legal frameworks, the study looked at the availability of regulations and guidelines which are key tools for law enforcement. Two (2) indicators assessed the existence of regulations and guidelines and the existence of the mechanisms for making the guidelines legally binding such as publication in the Government Gazette. Whereas data for Burundi was not provided, all the remaining NMRAs in the region have regulations and guidelines which govern the industry and stakeholders in undertaking their business. In addition, the study showed that each NMRA had in place mechanisms for making the existing guidelines legally binding as indicated in **Table 3.2** and illustrated in **Figure 3.2.**

The limitation of using these indicators is that they do not explore in more depth the type of regulations and guidelines being used. Neither do the indicators provide information on the level of enforcement and its impact on improving medicines regulation in a country. There is a need to further investigate the type of regulations, guidelines and other regulatory tools that each of the countries has in place when they came into force and the level of enforcement. This will assist in determining how effectively the law is being implemented.

Suffice to say that there is a progressive trend in terms of development of regulations and guidelines in the EAC Partner States. While baseline data showed three out of the six (50%) NMRAs had regulations and guidelines, in end-line data, 5 of 6 NMRAs (83%) reported having regulations and guidelines in place.

Table 3. 2 Regulations and Guidelines in the EAC Partner States; 2011/12 – 2014/15

	National Medicines Regulatory Agency					
Indicator	**Burundi**	**Kenya**	**Rwanda**	**Tanzania**	**Uganda**	**Zanzibar**
Existence of regulations and guidelines to govern regulation of medical products	-	Yes	Yes	Yes	Yes	Yes
Existence of a mechanism for making guidelines legally binding						
a. Publication in Government Gazette	-	Yes	Yes	Yes	Yes	-
b. Regulations	-	Yes	Yes	Yes	Yes	Yes

NB: *- = No data available/submitted*

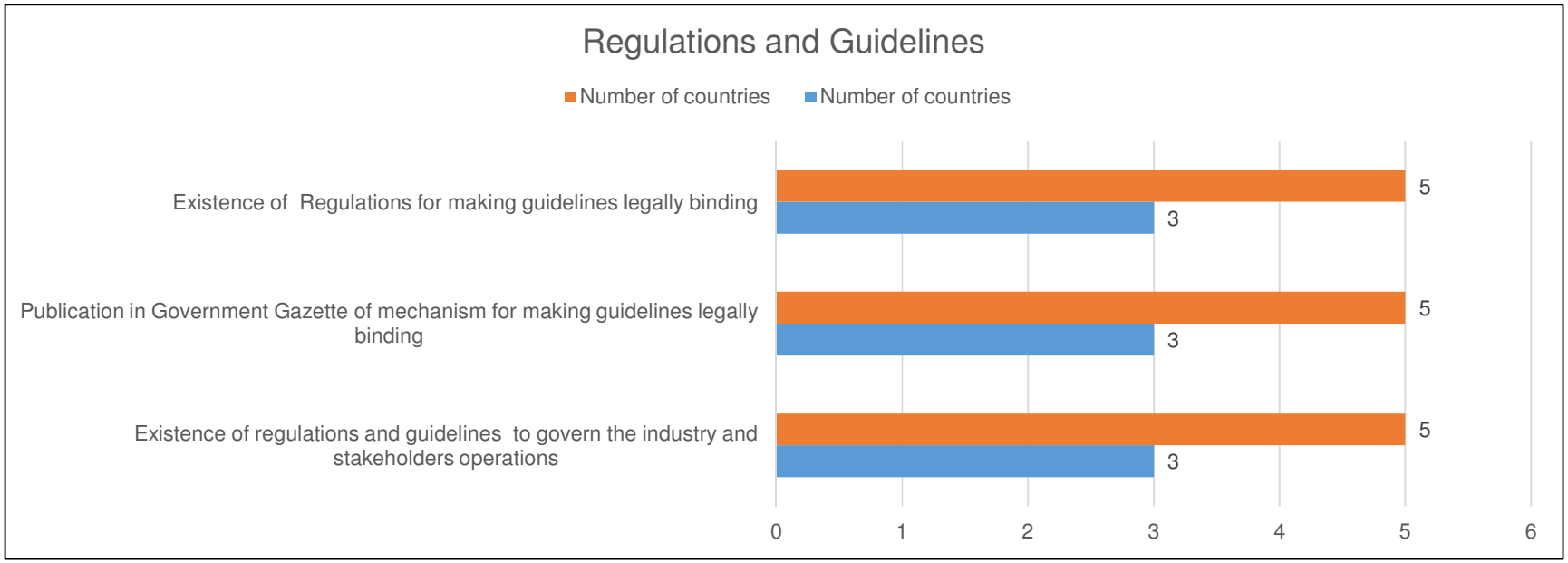

Figure 3.2: Trends in developing regulations and guidelines in the EAC Partner States (excluding Burundi); 2011/12 – 2014/15

3.3 REGULATORY GOVERNANCE

Governance refers to availability of policies in an organization and the ability to continuously monitor their proper implementation by the members of the governing body including the balance of power and the associated accountability of its members [59]. According to WHO appropriate NMRAs organizational structures which are autonomous, full-fledged departments, with statutory authority (Boards or Commissions) are key for ensuring independence, transparency and accountability in decision making [14]. These structures including the establishment of quality management systems facilitate the ability of the NMRAs to effectively fulfil their mandate in a transparent and accountable manner [14].

In this research, NMRA Governance was measured using **two (2) sub-indicators**; the level of NMRA autonomy, and availability of structures to support the NMRA decision-making process. According to the indicators' guidance, an autonomous agency means a financially and operationally independent body from other government bodies but accountable to public, with powers to recruit its own staff [43]. The level of autonomy was assessed based on full autonomy, semi-autonomy or a department under the Ministry of Health and the existence of Board and Technical/Experts Committee to govern NMRA operations. The existence of an NMRA Governing Board and its nature, the existence of Technical/Expert Committee(s) responsible for assessing applications for registration of pharmaceutical products and GMP inspections, an NMRA decision-making entity, and frequency of Technical Committees and Board meetings per annum were used as sub-indicators to measure availability of structures to support the decision-making process.

A baseline study revealed that TMDA, ZFDB and Kenya Pharmacy and Poisons Board (PPB) were semi-autonomous entities and that the head of PPB also served as a Chief Pharmacist combining both regulatory and policy roles as the technical arm of the Ministry of Health [35]. For Rwanda and Burundi, regulatory functions were administered by the respective Ministries of Health Departments. For TMDA (Tanzania),

KPPB (Kenya) and the NDA (Uganda), the agencies had powers to charge fees for regulatory services and received very little or no government subvention [15,39].

While details of funding source are provided under a separate NMRA financing section in this research, assessment of the level of autonomy of NMRAs still showed diversity in modalities in which the NMRA are governed within the EAC Partner States. Currently three (3) NMRAs are operating as semi-autonomous agencies namely; the Tanzania Medicines and Medical Devices Authority (for Tanzania mainland), Zanzibar Food and Drug Agency (ZFDA) and Kenya PPB while Uganda National Drugs Authority (NDA), is fully autonomous. In addition, the Rwanda Food and Drugs Authority is established as a semi-autonomous agency under the Rwanda Food and Drugs Law of 2013 which came into force in 2018 (The law nº 003/2018 of 09/02/2018). Furthermore, the National Pharmaceuticals Regulation Law of Burundi which was under consideration by the national Parliament provides for the establishment of a semi-autonomous NMRA to be called Drug and Food Regulatory Authority of Burundi (ABREMA) [60].

During the studied period, Governing Boards for NMRAs were present in all EAC Partner States except for Rwanda and Burundi. The functions of the Boards are either advisory in nature as is the case for Tanzania Mainland and Tanzania Zanzibar; strategic in Uganda, while in Kenya the Board is executive in function. It was further reported that the technical or expert committee(s) responsible for assessing applications for registration of pharmaceutical products and GMP inspection were in existence in Burundi, Kenya, Tanzania and Uganda, and absent in Rwanda and Zanzibar. While in Uganda the Committee on the National Formulary (CNF) is the decision-making entity, the situation varies from country to country. In Kenya, the Governing Board is the decision-making body while in Rwanda, it is the Director General for Clinical and Public Health Services (Rwanda). On the other hand, in Tanzania Mainland the Director General makes the final decision based on guidance by Technical Committees and in Burundi, the Technical or Expert Committees is responsible for decision making. In all cases, whether the Head of Agency or the Board makes the decision, they are accountable to the Minister of Health.

The frequencies of technical committee(s) and Board meetings were also assessed as illustrated in **Figure 3.3.** The highest reported number of Board meetings was in Uganda with six (6) meetings per annum, followed by Kenya having four (4) Board meetings per annum and the least was Zanzibar which reported three (3) Board meetings per annum. It was also indicated that the technical or expert committee on registration of medicines holds weekly meetings in Kenya, while in Tanzania and Uganda the meetings were held quarterly. Furthermore, the Technical or Expert Committee on GMP Inspection was reported to be meeting monthly in Kenya and Uganda, quarterly in Tanzania and twice in Burundi.

Table 3.3 provides a detailed analysis of the NMRAs governance framework including the level of autonomy, the existence and type of Boards; and frequency of Technical Committee and Board meetings. While the frequency of meetings may not reflect much in terms of regulatory decisions made, more information is needed to ascertain the attribution of the work of these committees to faster approval of medical products in a country. Information on adherence to meeting schedules by the Board and Technical Committee; number of products considered by the Board or Committee over a given period and regulatory decisions made needs to be further assessed to determine the approval timelines. More research is needed to determine the correlation between the frequencies of Board or Committee meetings with the time to approval of medicines.

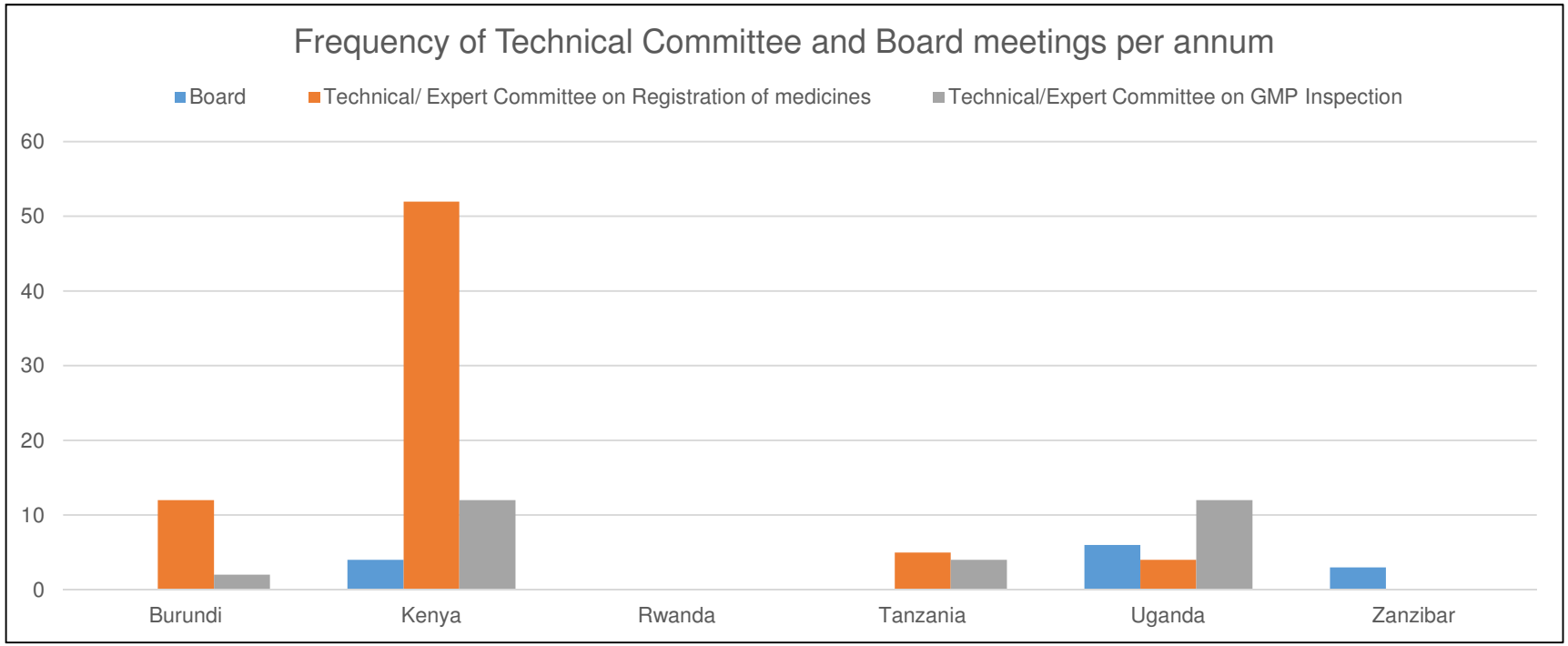

Figure 3.3: Frequency of Board and Technical Committee Meetings; 2011/12 – 2014/15Figure 3. 3: Frequency of Board and Technical Committee Meetings; 2011/12 – 2014/15

Table 3. 3 NMRA Governance in the EAC Partner States; 2011/12 – 2014/15

	National Medicines Regulatory Agency					
Indicator	**Burundi**	**Kenya**	**Rwanda**	**Tanzania**	**Uganda**	**Zanzibar**
NMRA level of autonomy	Department within the Ministry of Health	Semi-Autonomous	Semi-Autonomous	Semi-Autonomous	Autonomous	Semi-Autonomous
Existence of NMRA Governing Board	No	Yes	No	Yes	Yes	Yes
Nature of Board functions	NA	Executive	NA	Advisory	Strategic	Executive
Existence of Technical/Expert Committee(s) responsible for assessing applications for registration of pharmaceutical products and GMP inspection	Yes	Yes	No	Yes	Yes	No
NMRA Decision making entity	Technical/ Expert Committee	Governing Board	DG Clinical and Public Health Services	Director General	Committee on the National Formulary (CNF)	Governing Board
Frequency of Technical Committee and Board meetings per annum						
a) Board	NA	4	NA	-	6	3
b) Technical/Expert Committee on Registration of medicines	12	52	NA	5	4	None
c) Technical/Expert Committee on GMP Inspection	2	12	NA	4	12	None

NB: *- = No data available/submitted*

3.4 NMRA FINANCING

Adequate and sustainable financing of NMRAs is key to ensure circulation of good quality, safe and efficacious medical products in a market. This section focused on the assessment of factors affecting NMRAs funding in the six NMRAs in the EAC region. Five indicators were used namely; policy on NMRAs funding; level of autonomy; reliability of funding (annual budgets against actual funding); sources of revenue; and expenditure patterns.

Funding policies and laws of NMRAs: All six NMRAs provided data on their national medicines policies (NMPs) and medicines laws. While all the NMPs emphasise the need for effective regulation of medical products, policy commitment on funding NMRAs varies across countries. For semi- or fully autonomous NMRAs such as the Tanzania Medicines and Medical Devices Authority (TMDA), the National Drug Authority in Uganda (NDA), the Pharmacy and Poisons Board in Kenya (PPB), the Rwanda Food and Drugs Authority (Rwanda FDA) and the Zanzibar Food and Drug Agency (ZFDA), the laws provide for collection of fees from industry and its utilization to perform regulatory services [53–57]. However, in Burundi, the NMRAs was observed to be fully reliant on government funding during the studied period [52].

Level of NMRA Financial Autonomy: There has been a progressive transformation of the level of financial autonomy of NMRAs in the EAC region over the study period (Table 3.4). While Burundi NMRA is not autonomous, the Bill to transform the existing unit to an autonomous agency is at an advanced stage of consideration by her parliament [61]. In Rwanda on the other hand, the Food and Drugs Act of 2013 has been enacted to establish the Rwanda Food and Drugs Authority as a semi-autonomous agency [54]. In Zanzibar, the former Zanzibar Food and Drugs Board (ZFDB) has been transformed into Zanzibar Food and Drugs Agency (ZFDA) by the Zanzibar Food, Drugs and Cosmetics Act number 2 of 2006 as amended with financial autonomy under the oversight of an Advisory Board [56]. The existing laws in Kenya, Uganda and Tanzania-Mainland, provide for financial autonomy and empower the respective NMRAs to collect and utilise fees for services rendered [53,55,57].

Table 3. 4: Level of NMRA autonomy in the EAC partner states between the years 2011 and 2015.

Indicator	National Medicines Regulatory Agency					
	Burundi	**Kenya**	**Rwanda**	**Tanzania**	**Uganda**	**Zanzibar**
NMRA's level of autonomy	Department within the Ministry of Health	Semi-Autonomous	Semi-Autonomous	Semi-Autonomous	Autonomous	Semi-Autonomous
Medicine Law	Republic of Burundi. Decret No. 100/150 du 30 September 1980 portant Organizatio n de l'exercise de la Pharmacie au Burundi. 1980.	Republic of Kenya. The Pharmacy and Poisons Act, Chapter 244. 1957, as amended in 2009.	Republic of Rwanda. Law No. 47/2012 of 14/01/2013 relating to the Regulation and Inspection of Food and Pharmaceuti cal Products. 2013	United Republic of Tanzania (Mainland). Tanzania Food, Drugs and Cosmetics Act, Cap 219. 2003, as amended in 2004, 2014 & 2019	Republic of Uganda. The National Drug Policy and Authority Act. 1993.	United Republic of Tanzania (Zanzibar). The Zanzibar Food, Drugs and Cosmetics Act. No. 2 of 2006 as amended in 2016

NMRAs' annual budgets: The average total annual budget for all the countries for the period 2011-2015 ranged from USD 824,328.67 to USD 10,724,536.5 as shown in **Figure 3.4,** with Zanzibar and Uganda NMRAs having the lowest and highest average total annual budgets respectively. The NMRAs in Tanzania and Kenya exhibited almost similar average annual budgets, while the data for this indicator was not available for Burundi and Rwanda NMRAs. When compared to their own baselines, the total annual budget of each NMRA approximately doubled over a duration of five years.

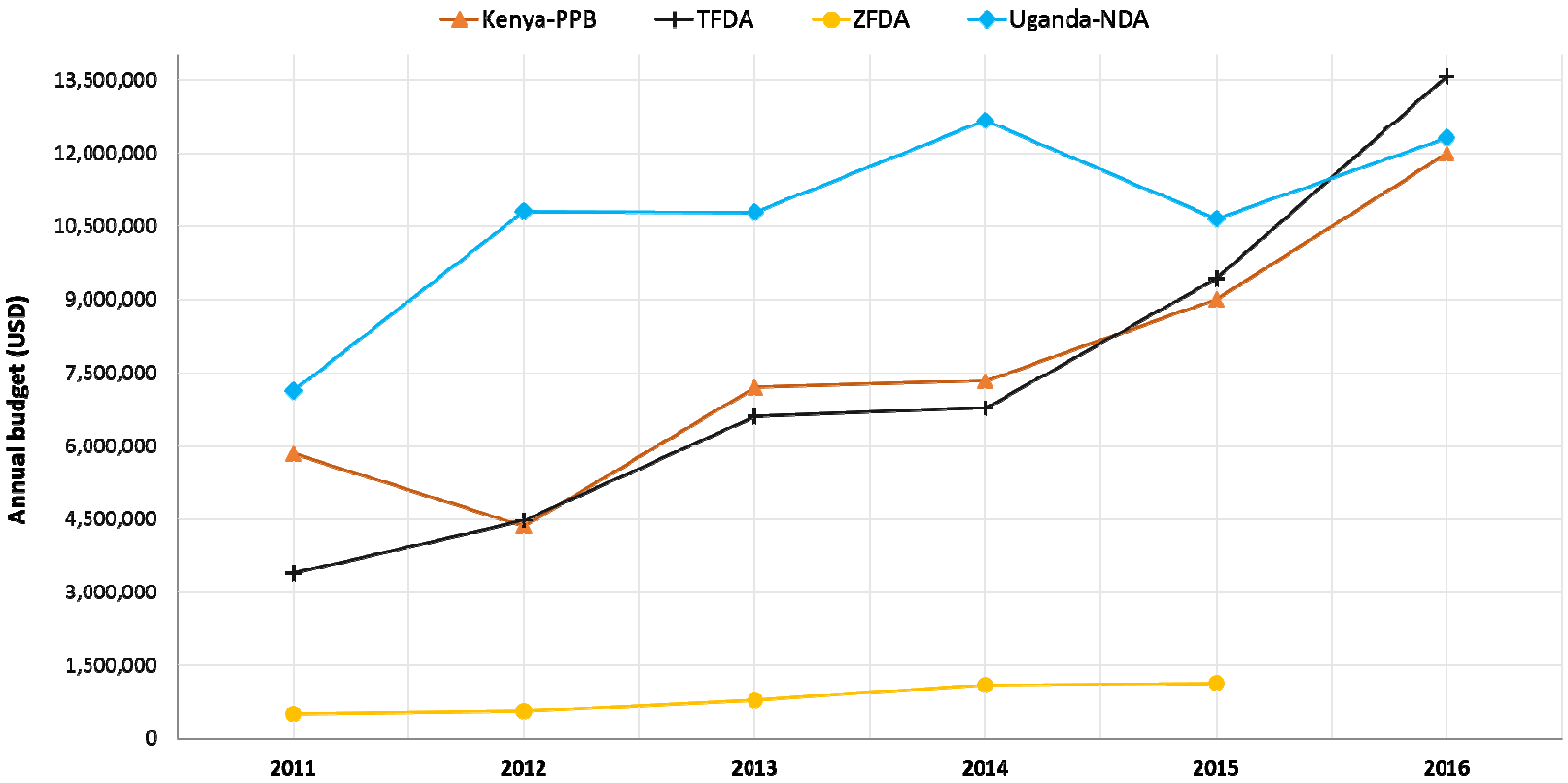

Figure 3.4: Trends in East African community national medicines regulatory authorities' annual budgets, 2011/12-2015/16.

NMRAs' annual funding: Comparison of the total annual budget against actual funding per annum shows an average of 54.8% (USD 458,970.11); 98.7% (USD 10,302,295.25) and 100% (N= USD 7,375,802.08) for Zanzibar Food & Drugs Agency (ZFDA), Uganda National Drug Authority (NDA) and Tanzania Medicines and Medical Devices Authority (TMDA) respectively, for years 2011-2015. However, data from Kenya and Rwanda under this aspect was not available **(Fig 3.5)**. The 54% funding for ZFDA may entail either a problem with setting an unrealistic budget or simply that funding was inadequate to support NMRA activities.

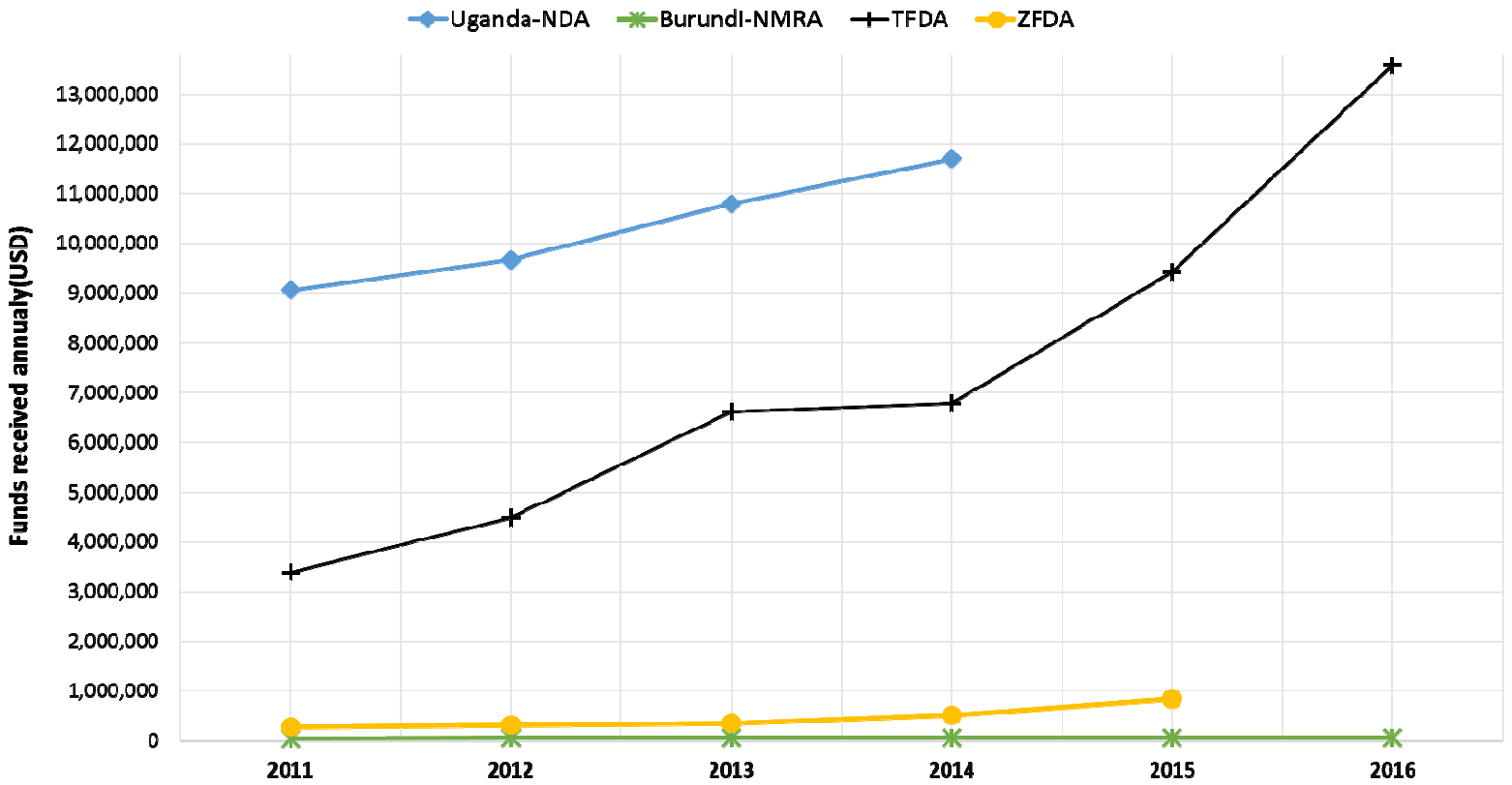

Figure 3.5: Trends in annual funding among national medicines regulatory authorities in the East African Community 2011/12-2015/16

Sources of revenue for NMRAs:

Assessment of the various sources of funds received by the NMRAs indicated governments, industry fees, and donors to be the major funding sources across all NMRAs as shown in **Fig 3.6**. It is important to note that the PPB in Kenya only provided data on annual budgets without indicating the sources of its revenue. For the NMRAs in Tanzania-Mainland (TMDA) and Uganda (NDA), industry fees were observed to be the major source of funds. On average, industry fees contributed up to 73.20% and 98.25% of the total annual revenue for TMDA NDA respectively. For Zanzibar (ZFDA) and Burundi NMRAs, the governments were observed to be the main sources of revenue with Burundi relying solely on the government funding while for ZFDA, on average government contributes 50.40%, industry fees 40.60% and the remaining 9% of the total revenue is from donors and other sources.

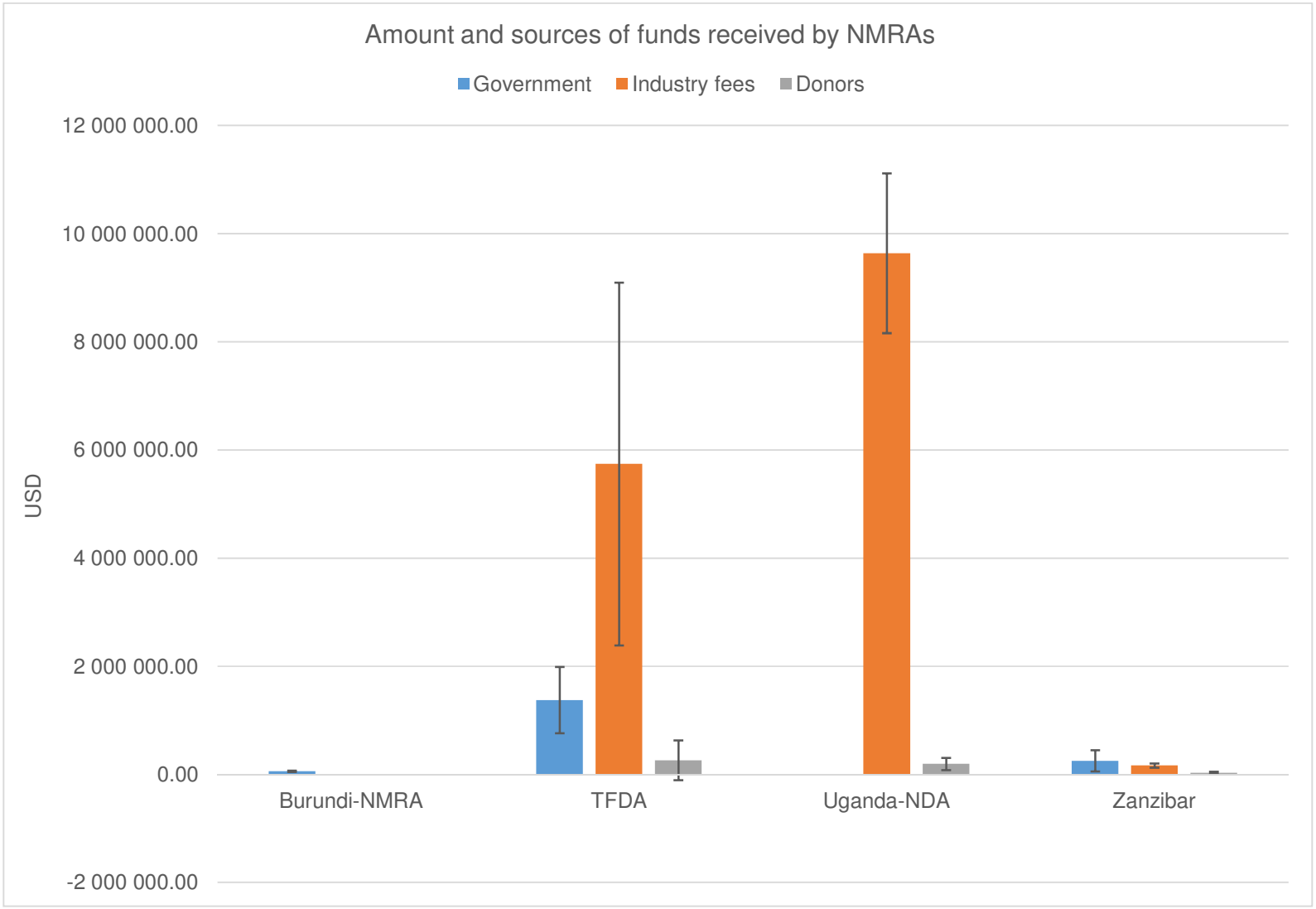

Figure 3.6: Annual mean amounts (in USD ± SD) and sources of funds received by national medicines regulatory authorities 2011/12 -2014/15.

Funds received from donors indicated a high degree of variation, with some NMRAs receiving funding only once over a five year duration, while others received fluctuating amounts with no remarkable trends. Funding partners most cited include the Bill and Melinda Gates Foundation (BMGF), World Health Organisation (WHO), United Nations Industrial Development organization (UNIDO), Clinton Health Access Initiative (CHAI), United Nations International Children's Fund (UNICEF), Management Sciences for Health (MSH), World Bank, Trademark East Africa Limited (TMEA), German Corporation for International Cooperation (GIZ), Global Fund, the United States Pharmacopoeia (USP) and the United States Agency for International Development (USAID) just to mention a few. On average, the overall contribution of funds received from donors by each NMRA was the least among other sources of financing.

NMRAs' expenditure: Observation of expenditure patterns indicated operational costs to be the major expense in the majority of the NMRAs, followed by salaries and infrastructure development as shown in **Fig 3.7**. This is also explained by the observed increase in the number of staff among the NMRAs from which the annual number of staff could be obtained **(Fig 3.8).** The PPB in Kenya indicated the highest degree of average expenditure across all three categories, with the least average expenditures being marked by the Burundi NMRA. Data from Rwanda and Zanzibar NMRAs were not available for this indicator. The operational costs on average increased considerably across all the NMRAs during the studied period.

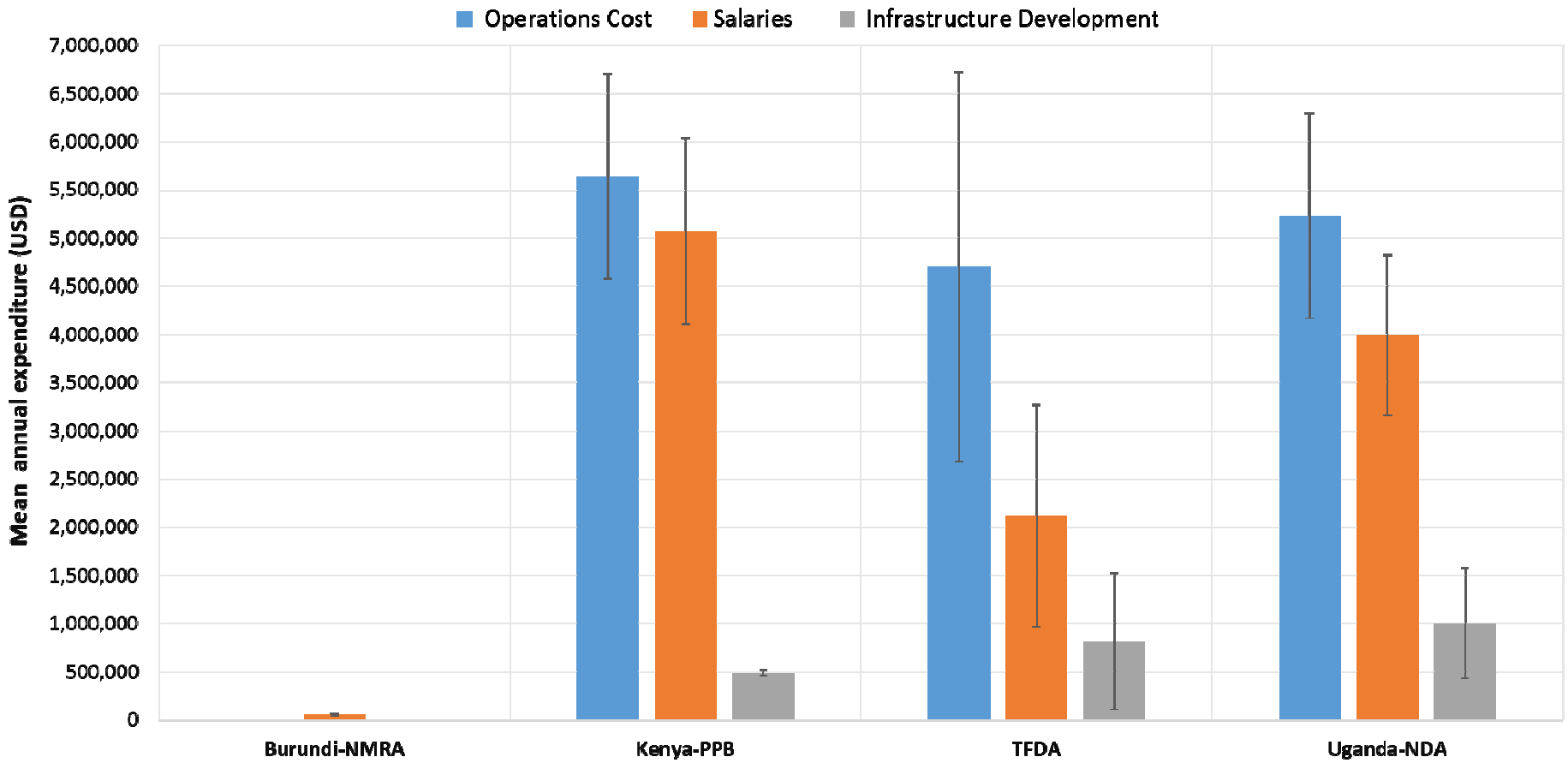

Figure 3.7: Mean annual amounts and main areas of expenditure in USD± SD by the national medicines regulatory authorities in the EAC, 2011/12 -2015/16.

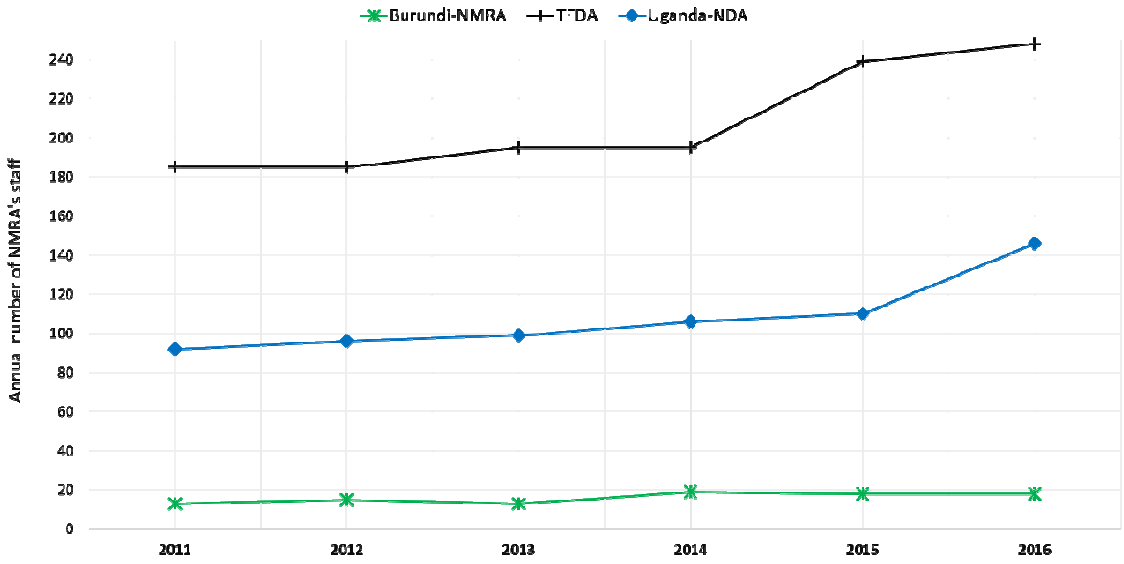

Figure 3.8: Annual trend in the number of staff per National medicines regulatory authority.

In this study, data on population size, the number of pharmaceutical establishments and the pharmaceutical market size was intended to determine the level of investment (in terms of financial and human resources) required to control the market. However, only Burundi provided data on pharmaceutical market size making analysis and comparison between countries difficult. The inability of the indicator to provide data on funding for NMRAs participation in the EAC MRH Project is a limitation that needs to be addressed in future evaluations.

3.5 MEDICINES REGISTRATION AND GMP INSPECTION SYSTEMS

Medicines registration system: A medicines registration system means a system that subjects all medical products to pre-marketing evaluation and issuing marketing authorization for ensuring that products conform to required standards of quality, safety, and efficacy [62]. Several indicators were used to measure the existence of a registration system in a country. They include; i) legal mandate to register medicines; ii) availability of a system for receiving applications, evaluating and providing marketing

authorisation for medicines; iii) availability and use of EAC harmonized guidelines for registration of medicines; iv) availability and use of standard operating procedures (SOPs) for joint review of dossiers; v) availability of competent staff (assessors) with the requisite education, training, skills, and experience; and vi) participation of the NMRA in the regional process for joint review of dossiers and subsequent decision-making process in a country. The number of products registered and timelines for registration based on EAC joint dossier review was also used as additional indicators.

Findings indicated that all the six (6) NMRAs have a legal mandate to register medicines and have a system to manage applications from receipt of dossier to the issuance of marketing authorization. In addition, all the NMRAs use the EAC harmonized guidelines for registration of medicines which came into force in 2015 including the respective SoPs for a joint review of dossiers [63]. Furthermore, it was observed that each NMRA has participated at least once in the EAC joint review of dossiers for registration medicines from the year 2015 with Zanzibar and Tanzania indicating the highest number of joint assessment participations (3).

Although the EAC Partner States participate in the regional joint reviews using respective NMRAs experts and harmonized guidelines and standards for assessment, the time taken to register a product based on the outcome of the joint review process varies from country to country. In addition, the number of products registered following the regional review process also varied. For instance, out of fifteen (15) applications which were received through the regional procedure, TFDA registered all the products; KPPB 13/15; Burundi 1/15; Rwanda 9/15; Zanzibar 1/15, and Uganda 7/15.

Policies on abridged procedures for registration of medicines exist in Kenya, Tanzania and Uganda while it is not the case for Burundi, Rwanda and Zanzibar. The abridged procedure entails the NMRAs reliance on regulatory decisions made by other agencies by not conducting a full dossier assessment. This is an indication of efficiency in dossier review processes and subsequent decision-making as it serves time for a full dossier review. Tanzania Mainland's NMRA is indicated to have the oldest policy for abridged review of dossiers, which came into existence in 2011.

A high degree of variation was observed on the reference regulatory standards used on the abridged procedure for registration of medicines among the NMRAs. Even though there was no policy on an abridged procedure for registration of medicines in Zanzibar, the ZFDA and Kenya PPB indicated that they used WHO-PQ as reference standard for abridged procedure. Moreover, the Uganda NDA reported the use of EAC joint review outcome, Stringent Regulatory Authorities (SRAs) and the WHO-PQ as basis for abridged procedure while Rwanda relied on EAC and WHO-PQ as reference standards. The reference regulatory standards for abridged registration procedure in Burundi and Zanzibar were not made available.

GMP Inspection System: GMP is defined as a system for ensuring that products are consistently produced and controlled according to quality standards thereby minimizing the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product [64]. GMP as an integral part of the registration system was measured using Seven (7) indicators. They include a legal mandate to conduct GMP inspection, availability of guidelines and standard operating procedures for GMP Inspections, availability of competent staff (GMP Inspectors) with the requisite education, training, skills, and experience, clear job descriptions for staff (elaborate duties, functions and responsibilities). The use of regional harmonized guidelines for GMP inspection, the level of country's participation in joint regional inspections, uptake of joint GMP inspection as basis for national regulatory decision and use of desk review/document review method as basis for regulatory decision (reliance on other NMRAs decisions), was also assessed.

All six (6) NMRAs have a legal mandate to conduct GMP inspection. Except for Burundi NMRA, the remaining NMRAs reported to be conducting inspections of manufacturing sites. While Kenya, Tanzania and Uganda NMRAs had conducted inspections since the baseline study period, Rwanda and Zanzibar NMRAs only started in 2015. Moreover, All NMRAs indicated using the EAC harmonized guidelines for GMP inspection from 2015 when they came into force [60]. Each NMRA reported having participated at least once in the EAC joint inspections. In addition, Rwanda, Uganda and Zanzibar employ a reliance models by using GMP inspection reports from other agencies such as EAC,

SRAs, PICs, US-FDA, and/or WHO-PQ Programme [65]. Zanzibar NMRA reported to have made decisions on GMP status of a manufacturing site using the EAC GMP inspection report; and WHO-Prequalification GMP inspection reports even though there was no written policy in place [65]. Rwanda, on the other hand, uses EAC, PICs & WHO-PQ as reference regulatory standards for document review while Uganda uses EAC, WHO-PQ and US-FDA standards. A policy was found not to be in place in the NMRAs of the remaining Partner States [65].

Table 3.5 provides a detailed analysis of the status of registration and GMP inspection system in the 6 NMRAs in the EAC region. Please note findings on availability of competent staff are presented on a separate **Table 3.6.**

Table 3. 5: Medicines Registration and GMP Inspection Systems in the EAC Partner States NMRAs; 2011/12 – 2015/16

INDICATOR	National Medicine Regulatory Agency					
	Burundi	Kenya	Rwanda	Tanzania	Uganda	Zanzibar
Legal mandate to register medicines	Yes	Yes	Yes	Yes	Yes	Yes
Availability of a system for receiving applications, evaluating and providing marketing authorisation for medicines	Yes	Yes	Yes	Yes	Yes	Yes
Availability and use of EAC Harmonized guidelines for registration of medicines	Yes	Yes	Yes	Yes	Yes	Yes
Year EAC Harmonized Guidelines for Registration of Medicines came into force	2015	2015	2015	2015	2015	2015
Participation in EAC joint assessments	Yes (2015)	Yes (2015)	Yes (2015)	Yes (2016)	Yes (2015)	Yes (2015)
Number of joint assessments participated by NMRA	1	1	1	3	1	3
Existence of policy on abridged procedure for registration of medicines	No	Yes	No	Yes (2011)	Yes (2016)	No. It is happening but there is no written policy yet.
Reference regulatory standard used on abridged procedure for registration of medicines	None	WHO-PQ	EAC & WHO-PQ	In-house SOP	EAC, SRAs & WHO-PQ	WHO-PQ
*Number of products registered based on EAC joint dossier review***	1/15	13/15	9/15	15/15	7/15	1/15
*Time taken to register medicines based on joint review outcome***	N/I	N/I	N/I	N/I	N/I	N/I
Legal mandated to conduct GMP inspection	No	Yes (2011)	Yes (2015)	Yes (2011)	Yes (2011)	Yes (2015)
NMRA using EAC Harmonized guidelines for good manufacturing practice (GMP)	No	Yes	Yes	Yes	Yes	Yes
Year EAC GMP guidelines came into force	-	2015	2015	2015	2015	2015
Participating in EAC joint inspections	Yes (2014&16)	Yes (2015)	Yes (2015)	Yes (2015)	Yes (2012)	Yes (2012)
Availability of policy on GMP assessment of pharmaceutical manufacturing sites	No	No	Yes	No	Yes	No. It is happening but there is no written policy

using document review						yet.
Reference regulatory standard used for GMP document review	NA	NA	EAC, PICs & WHO-PQ	NA	EAC, WHO-PQ, US-FDA, EMA, PICS Inspection Reports	EAC GMP inspection report, WHO-Prequalification GMP inspection reports-

NB: Year in the bracket indicating the time from which the indicator started to apply NB= 2016 data (not average), - = No data available/ submitted*; ** *= Secondary data EAC MRH Project SC Meeting Report (2018); N/I = Not indicated*

NMRA Human Resource Capacity: Availability of the requisite number of staff with relevant qualifications, skills and knowledge to perform core regulatory and managerial functions is a critical factor for NMRA performance. The human resource capacity of the NMRAs in the EAC Partner States was evaluated using **14 indicators** as seen in **Table 3.6** over a 5 years duration.

The mean number of NMRA staff was observed to range from a minimum of 16 in Burundi to a maximum of 208 in Tanzania-Mainland. The staff was observed to be from various categories and operational units of the NMRAs. An overall annual increase in the total number of staff was observed in Burundi (16 – 18), Tanzania (185 – 248) and Uganda (96 - 146), whereas only data for 2016 were made available for Rwanda (31) and Zanzibar (89).

The number of product assessors in the NMRAs ranged from 6 in Burundi to 29 in Tanzania-Mainland in 2016, with the majority of the NMRAs observed to have more than 10 product assessors in place. Uganda reported an average of 21 product assessors per year for a five-year period. The number of GMP inspectors reported to be present in each partner state was between 2 and 22, with the majority of the NMRAs having less than 10 GMP inspectors. Apart from Burundi where there was no data provided, almost all NMRAs reported having been making their regulatory decisions based on both internal and external scientific expertise. External scientific experts are drawn from academic institutions attached to teaching hospitals.

Only NMRA's from Kenya, Uganda and Tanzania reported having in place a human resource development plan and frameworks for staff skills audit and competence assessment. Furthermore, an annual training programme for staff was reported to be in place in Tanzania-Mainland and Uganda from 2010 but was absent in Kenya over the entire study period.

The EAC regulatory training programmes reported to have contributed to the training of 4 to 20 NMRA staff across all partner states in 2016. Only Burundi and Zanzibar NMRAs reported to have never provided experts (trainers) to train staff under the EAC

harmonization scheme over the entire study period; the remaining NMRAs reported to have provided between 2 and 4 trainers to the scheme. Regarding the participation of the staff from the NMRAs to the WHO-PQ scheme, at most 3 staff from a single NMRA were observed to have participated in the scheme.

Table 3. 6 NMRA Human Resource Capacity in the EAC Partner States National Medicines Regulatory Authorities; 2011/12 – 2015/16

INDICATOR	National Medicine Regulatory Agency					
	Burundi	Kenya	Rwanda	Tanzania	Uganda	Zanzibar
Mean total number of NMRA staff	16.60±2.51	-	31*	208.2±27.8	111.40±20.12	89*
Mean number of product assessors	6*	20*	10*	29*	21±0.0	11*
Mean number of GMP inspectors	2*	22*	4*	14*	7	6*
Regulatory decisions purely based on internal or scientific assessment	-	Yes	Yes	Yes	Yes	Yes
Mean number of external expertise used outside NMRA	-	0	0	0	0	0
NMRA human resource development plan is available	No	Yes (2010)	No	Yes (2010)	Yes (2010)	No
A plan providing for skills audit and competence assessment of staff	N/A	Yes	N/A	Yes (2010)	Yes (2010)	N/A
Availability of an annual training programme for staff	No	-	No	Yes (2010)	Yes (2010)	No
Mean number of staff trained per annum	2*	-	N/A	56.3±19.6	35*	N/A
Mean number of staff trained in the EAC regulatory training programmes	16*	-	12*	5*	20*	4*
NMRA provides experts (trainers) to train staff under the EAC Harmonization Scheme	No	Yes (2010)	Yes (2010)	Yes (2010)	Yes (2010)	No
Mean number of trainers provided by NMRA	0	3*	2*	3.3±0.6	-	0
Mean number of NMRA staff have participated in WHO-PQ Training programme	2*	0	3*	1.7±0.8	3*	1*
Mean number of NMRA staff that have participated in training programmes organized by other partners	2*	5*	2*	3.0±0.9	-	2*

NB: *= 2016 data (not average), - = No data available/submitted

Efficiency of Registration System: Efficiency of registration systems is a measure of time taken to make a final regulatory decision on a product by the NMRA [93]. According to the study indicators tool, the proportion of NMRAs who made regulatory decisions within a prescribed time based on regional reports or national assessment/s is used as an indication of the efficiency of the review process. The assessment used a combination of 6 sub-indicators under indicator 4 including applications received per annum, applications carried over from previous reference year(s), medicines registered by the NMRA per annum, availability of mechanisms for tracking registration timelines, average timeline ranges attained for fast-tracked products, and the average timeline range attained for normal review. The observation was done over a five year duration (2011/12-2015/16).

Table 3.7 provides detailed results on the status of each of the EAC NMRAs system for registration of medicines. The highest five years average of 800 new applications were received by the Tanzania-Mainland NMRA, followed by Uganda (458), Burundi (70) and Zanzibar (16). However, Kenya's NMRA reported 1,030 applications received compared to Rwanda's NMRA which reported having received a total of 833 new applications in the year 2016, as the only year's data was available.

It was further reported that Kenya's NMRA had a backlog of 1,000 applications carried over to 2016 whereas Rwanda's NMRA had a total of 575 applications carried over from previous years in the year 2016 alone. Findings from TMDA showed up to 980 applications being carried over in the year 2011 and decreasing year after year, reaching a minimum of 76 applications in 2016.

The five years average number of medicines registered per annum over the studied period was found to be highest in Kenya's NMRA which reported 514 products, followed by Tanzania (463), Uganda (344), Rwanda NMRA (175) and Zanzibar (6), while no products were reported to have been registered by the NMRA in Burundi over the entire studied period.

Three NMRAs reported to have a mechanism for tracking dossier applications, which were in place from the baseline year (2010/11) in Tanzania and Kenya, and later in Zanzibar during the year 2015. No mechanism was indicated to be in place in the

remaining Partner States. Furthermore, Kenya and Tanzania reported a range of 3 to 6 months in the registration of fast-tracked medicines, whereas for normal review, the average time of 12 months was reported by both NMRAs, in addition to Zanzibar. Secondary data further shows that the median timeline from dossier submissions to national marketing authorization in the EAC region was reduced to seven (7) months since implementation of joint dossier assessments compared to the previous 1 – 2 years [42]. It is important to note here that timelines provided by NMRAs are what has been set in the client service charter, further assessment is needed to determine the actual measured timelines for approval.

Table 3. 7 Medicines Registration System in the EAC Partner States NMRAs; 2011/12 – 2015/16

INDICATOR	**National Medicine Regulatory Agency**					
Mean ± SD numbers of Medicines:	**Burundi**	**Kenya**	**Rwanda**	**Tanzania**	**Uganda**	**Zanzibar**
Applications received per annum	70.0±42.0	1,030*	833*	799.7±275.2	457.80±148.73	16.00±18.89
Application carried over from previous reference year(s)	0.0±0.0	1000*	575*	443.0±301.4	-	0
Medicines registered by the NMRA per annum	0.0±0.0	514*	175*	463.0±224.6	344.40±243.87	6.20±4.76
Availability of mechanism for tracking registration timelines	No	Yes (2011)	No	Yes (2011)	No	Yes (2015)
Average timelines range attained for Fast-tracked products	-	3 months	-	4-6 months	-	-
Average timeline range attained for normal review	-	12 months	-	12 months	-	12 months

*NB: Year in the bracket indicating the time from which the indicator started to apply: *= 2016 data (not average), - = No data available/submitted*

3.6 INFORMATION MANAGEMENT SYSTEMS (IMS)

One of the EAC MRH Objectives is to have all the Partner States' NMRAs implementing common IMS for medicines registration in each of the EAC Partner States' NMRAs which is linked in all Partner States and the EAC Secretariat. A robust IMS is key for supporting the technical aspects of medicines regulation to facilitate efficiency and effectiveness of business processes, improve transparency; facilitate decision-making process, sharing and exchange of information among NMRAs and stakeholders; and timeliness of approval of registration decisions.

It should be noted that during the baseline survey in 2010/11, Tanzania-Mainland had an integrated system which was locally developed, and Kenya used SIAMED ® [36]. Uganda, on the other hand, used a combination of SIAMED®, ACCESS® and a locally developed software. Burundi had a manual IMS which was not functioning, Zanzibar had a functional manual registry and Rwanda had both a manual and electronic system. The method of capturing information in NMRA's in the EAC Partner States was variable and unreliable [58]. The challenges being that the electronic systems were not user friendly, they were difficult to integrate with other IMS platforms and could not automatically generate/print certificates or be linked to websites, and the manual systems were labour intensive [58].

This assessment was conducted to determine whether the NMRAs have attained requirements for an integrated IMS using **two (2) indicators;** functionality of IMS and attainment of AMRH IMS modules. The modules include Internal IMS, e-CTD to manage dossiers offline, e-CTD to manage dossiers through online applications, Integrated IMS at regional level, Licencing of premises, Import and export, and finance management system linked to regulatory functions such as registration, importations, licensing and inspections.

Secondary data was used to assess NMRA's performance in implementing the Seven (7) key IMS modules namely, Premises, Product, GMP, Inspection, Import & Export, Finance; and Report modules. A common IMS has been developed by Trademark East Africa (TEMEA) which is at different levels of development and implementation in

Burundi, Rwanda, Zanzibar and Uganda. The IMS in Kenya, Tanzania and Rwanda are fully functional; integrated to National Revenue Authority e-banking and/or Mobile Money while reports are customized according to the national and regional needs. Zanzibar has all the modules operational except for two i.e. the import and export and finance modules. Uganda IMS Modules are all operational except for the Finance Module. In Burundi, the Product, Inspection and Import & Export Modules are not functional while for the EAC Secretariat, only the Report Module is functional as indicated in **Table 3.8.**

The practice of sharing regulatory information with other NMRAs in the EAC region was indicated to be an on-going activity in the majority (5/6) of the Partner States, with exception of Burundi NMRA. Only the Kenya NMRA reported their IMS to be linked with other NMRAs in the region. None of the NMRA-IMS was linked to the EAC Secretariat as indicated in **Figure 3.9.**

Table 3. 8 Different Levels of IMS Implementation by the EAC Partner Sates NMRAs; 2011/12 – 2015/16

NMRA Key Modules	PPB-Kenya	TFDA-Tanzania	ZFDB-Zanzibar	NDA-Uganda	PTF MINISANTE-Rwanda	DPML-Burundi	EAC
Premises Module	✓	✓	✓	✓	✓	✓	**X**
Product Module	✓	✓	✓	✓	✓	**X**	**X**
GMP Module	✓	✓	✓	✓	✓	✓	**X**
Inspection Module	✓	✓	✓	✓	✓	**X**	**X**
Import &Export Module	✓✓	✓	**X**	✓✓	✓✓	**X**	**N/A**
Finance Module	✓✓✓	✓✓✓	**X**	**X**	✓	✓✓✓	**N/A**
Report Module	✓✓✓✓	✓✓✓✓	✓✓✓✓	✓✓✓✓	✓✓✓✓	✓✓✓✓	✓✓✓✓

Key: *✓ - Fully Functional; ✓✓ - Fully Functional & Integrated to National Revenue Authority; ✓✓✓ - Fully Functional and Integrated to e-banking and/or Mobile Money; ✓✓✓✓ - Fully Functional & reports customized according to the national and regional needs;* ***X*** *– Non Functional*

Source: EAC Secretariat MRH Project Progress Report, 2015

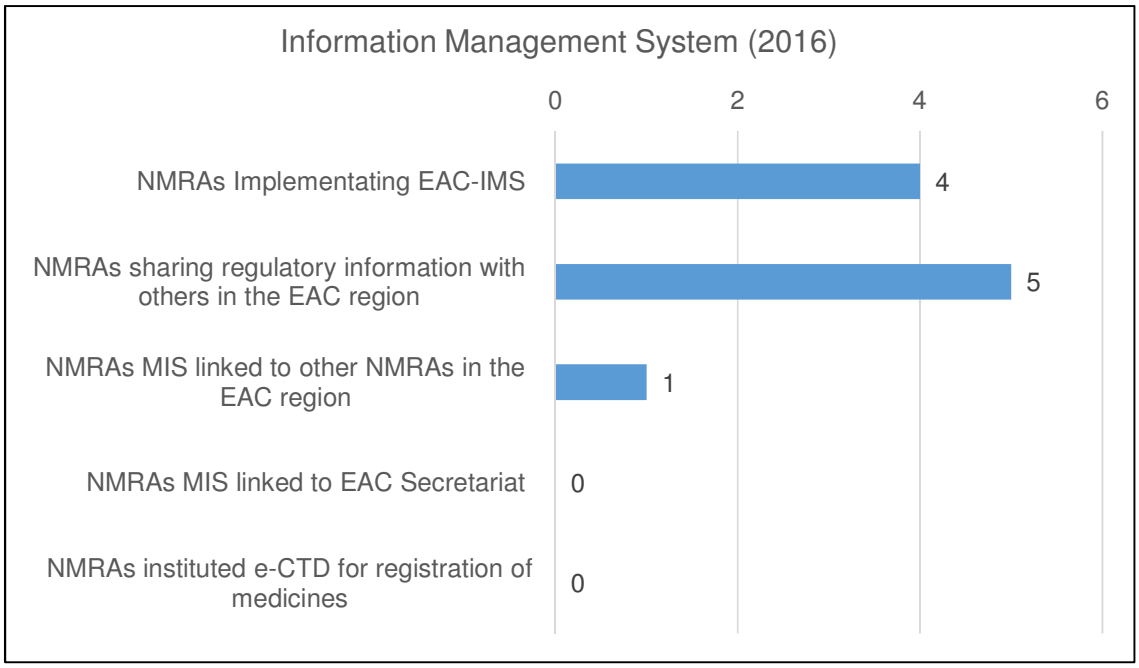

Figure 3.9: The Status of Implementation of Information Management Systems in the EAC Partner States NMRAs (2016).

Table 3. 9 Information Management System in the East African Community Partner States National Medicines Regulatory Authorities (2016)

	National Medicines Regulatory Agency					
Indicator	**Burundi**	**Kenya**	**Rwanda**	**Tanzania**	**Uganda**	**Zanzibar**
Implementation of EAC-IMS	No	Yes	No	Yes	Yes	Yes
NMRA sharing regulatory information with others in the EAC region	No	Yes	Yes	Yes	Yes	Yes
NMRA MIS linked to other NMRAs in the EAC region	No	Yes	No	No	No	No
NMRA MIS linked to EAC Secretariat	No	No	No	No	No	No
NMRA instituted e-CTD for registration of medicines	No	No	No	No	No	No

A comparison of IMS implementation status with baseline data shows a significant improvement in all the countries with Burundi and Zanzibar moving from manual to electronic systems. All the EAC NMRAs are now using a harmonized IMS with 5 out of 6 NMRAs sharing regulatory information amongst each other.

3.7 QUALITY MANAGEMENT SYSTEM (QMS)

Quality management (QM) is defined as the coordinated activities that direct and control an organization with regard to quality and refers to the appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality [68]. One of the most meaningful ways that NMRAs attempt to confirm the quality of their work is by becoming International Standards Organization (ISO) certified i.e. it is a measure of an agency's quality management system (QMS) as judged against the ISO standards [68]. Meeting the requirements for ISO certification is a globally recognized accreditation of the maturity and functionality of the quality management system of an organization, including medical products regulatory agencies.

The EAC MRH is promoting the implementation of QMS by the NMRAs based on the current ISO standard [69]. The overall objective of implementing QMS is to facilitate delivery of quality and consistent services to its customers. Attainment of QMS standards in the NMRA is an indication of management commitment and willingness to improve the quality of its regulatory services. Before the EAC MRH Project started Zanzibar, Burundi, Rwanda and Kenya had no system for quality management. Tanzania Food and Drug Authority was already implementing a QMS based on ISO 9001:2008 and Uganda had initiated the process of ISO certification by appointing a quality manager (EAC MRH Project Proposal (2010). In 2014, the QMS Expert Working Group (EWG), led by Kenya and assisted by WHO and Swissmedic developed a Compendium of QMS guidelines, requirements and Manual in line with ISO 9001:2008 and adopted by all EAC Partner States NMRAs [58]. However, following issuance of an updated version ISO 9001:2015 certification in 2015, all the NMRAs had to strive to reach the new standard [58].

Two (2) indicators were used to determine the level of implementation of EAC QMS in the NMRA based on ISO-9001 standard and the status of ISO-9001 Certification of NMRA medicines regulatory system. Evaluation of QMS implementation data from the EAC Partner States NMRAs indicated different levels of implementation as indicated in

Table 3.10. While Kenya, Tanzania, Uganda and Zanzibar NMRAs had started the implementation of QMS based on ISO-9001 standard, this was not the case for Burundi and Rwanda. Only the Tanzania Mainland NMRA was reported to have the ISO-9001 certification as of 2010.

Table 3. 10 Functional Quality Management System in the EAC Partner States NMRAs; 2011/12 – 2014/15

INDICATOR	National Medicine Regulatory Agency					
	Burundi	Kenya	Rwanda	Tanzania	Uganda	Zanzibar
Implementation of EAC QMS in the NMRA based on ISO-9001 standard	No	Yes (2011)	No	Yes (2014)	Yes (2014)	Yes
ISO-9001 Certification of NMRA medicines regulatory system	No	No	No	Yes (2010)	No	No

NB: Year in the bracket indicating the time from which the indicator started to apply

To date, Kenya, Tanzania, Zanzibar and Uganda's NMRAs are 9001:2015 ISO-certified, while Rwanda and Burundi are working toward 9001:2015 ISO certification. TMDA is the first in Africa to attain designation by WHO as a maturity level 3, denoting an agency with "a stable well-functioning and integrated system of oversight for medical products" [70]. It is important to note that once QMS is in place across the region, Partner States will have greater confidence in the quality of their neighbours' work, increasing trust and facilitating reliance on the documents and inspections of their regional NRMA colleagues. It is also important to recognise the achievement made by Kenya, Uganda and Zanzibar considering there was no QMS when the MRH Project started in 2012. PTF (Rwanda) is moving directly toward the attainment of the ISO 9001:2015 certifications while DPML (Burundi) implemented Quality Objectives and Standard Operating Procedures for some regulatory activities, including Medicines Evaluation and Registration.

3.8 PARTNERSHIPS AND COORDINATION

Various partners provide either technical, financial or policy support in the implementation of the EAC MRH Program. Coordination of such support is critical to

ensure effective implementation and cost-effective use of limited resources including alignment of interventions at national and regional levels.

The maximum number of partners providing support to the NMRAs on various regulatory functions at the country level was observed to be eight (8) for Kenya's NMRA in 2016. Other NMRAs had several partners ranging from 3 to 5, the minimum being in Burundi and Uganda NMRA as indicated in **Table 3.11.** In Rwanda for instance, Global Fund, USAID, GIZ, WHO (Country Office), AMRH Partners are the partners providing support. In Kenya on the other hand, EAC MRH, USP, TMEA, CHAI, PTB/GIZ, UNIDO and BMGF are the key partners providing support in medicines registration, laboratory analysis, GMP inspection and QMS. WHO was cited as the only partner providing technical and funding support to Burundi, but this information needs to be verified as other partners have been supporting Burundi in the area of medicine regulation. While Zanzibar did not provide information on partners and areas of support; TFDA indicated that WHO, UNIDO, CHAI, UNICEF, MSH, World Bank, IAEA, Global Fund, USP, JSI, EGPAF, Christian Social Services Commission/CSSC, EAC and NEPAD are mainly providing financial and technical assistance. Coordination in Tanzania-Mainland is done at the level of Ministry of Health. Further research is needed to determine how partners provide funding and technical support and whether it is short-term or long-term.

Eighty three percent (83%) of the countries reported having a mechanism for coordinating the partners as shown in **Figure 3.10.** This includes NMRAs in Burundi, Kenya, Rwanda, Tanzania and Uganda. As to how these partners are coordinated requires further exploration.

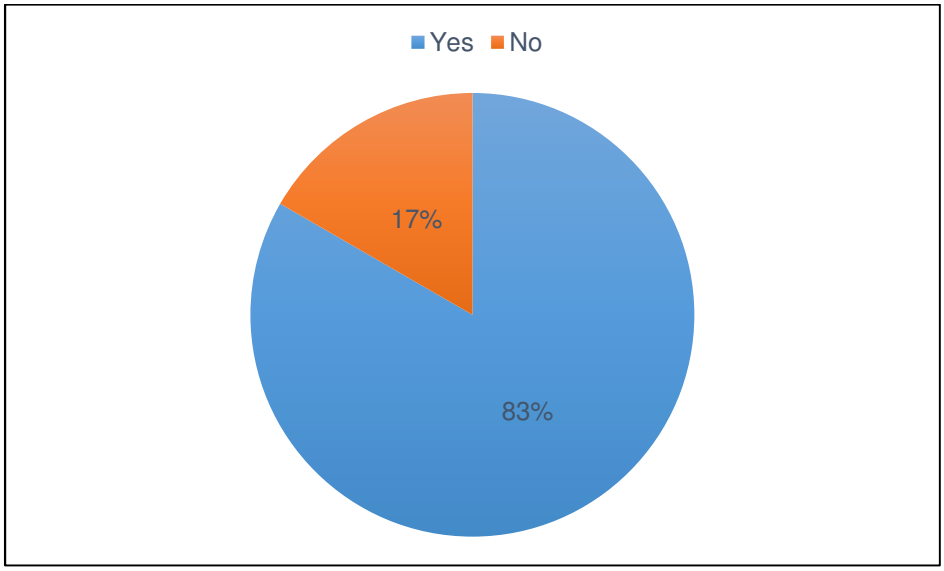

Figure 3.10: Status of Coordination of Partners by the EAC NMRAs; 2011/12 – 2014/15.

Table 3. 11: Partnerships and Coordination at the EAC Partner States NMRAs; 2011/12 – 2014/15

INDICATOR	National Medicine Regulatory Agency					
	Burundi	Kenya	Rwanda	Tanzania	Uganda	Zanzibar
Mean number of partners providing support to NMRA on various regulatory functions/mechanisms at country level	3*	8*	5*	4.4±2.4	3*	4.5
Type of support provided	-	Medicines registration, Lab analysis, GMP inspection, QMS	Financial and Technical	Medicines registration, Lab analysis, GMP inspection	Technical support	Technical support
Availability of Mechanism for coordination of partners at country level	Yes	Yes	Yes	Yes	Yes	No

*NB: *= 2016 data (not average), - = No data available/submitted*

3.9 LEVEL OF TRANSPARENCY AND ACCOUNTABILITY

Regulation is a public good which must seek to balance collective and individual interests. Regulatory policies of all kinds are, therefore, almost always accompanied by concerns about the transparency and accountability of government actions. Various mechanisms are instituted to ensure accountability of drug regulatory authorities including dissemination of guidelines and other relevant information to the industry and general public through newsletters and websites and/or publication in official gazettes. In addition, regulators are encouraged to maintain regular contacts with the industry to ensure accountability [47].

To determine whether a platform for information sharing with key stakeholders at the national and regional level has been established, this study looked into the level of transparency and accountability by assessing NMRAs use of IMS, communication and sharing of information with stakeholders and the general public including posting of regulatory policies on the website. In addition, the existence of a mechanism for engaging key stakeholders in instituting regulatory policies and NMRAs mechanisms for assessing the level of customer satisfaction was also assessed.

Stakeholders' engagement: the majority of NMRAs in the region indicated to have a mechanism in place for engaging key stakeholders such as pharmaceutical industries, researchers/scientists, academia, parliamentarians, civil society organizations and the public in instituting regulatory policies. Meetings, workshops and seminars were reflected in nearly all NMRAs to be among the mechanisms in place for engaging the stakeholders.

Moreover, the Pharmaceutical Manufacturers' Associations were indicated to be present in Kenya, Tanzania, and Uganda, while the Pharmaceutical Traders' Associations were reported to be available in Kenya, Rwanda, Tanzania and Zanzibar. Furthermore, the NMRAs in Kenya, Tanzania-Mainland, Tanzania-Zanzibar and Uganda reported the existence of mechanisms for assessing customers' satisfaction with the services offered by the respective NMRA as indicated in **Table 3.12**.

Table 3. 12 Stakeholders Engagement by the EAC Partner States NMRAs; 2011/12 – 2014/15

	National Medicines Regulatory Agency					
Indicator	**Burundi**	**Kenya**	**Rwanda**	**Tanzania**	**Uganda**	**Zanzibar**
Existence of a mechanism for engaging key stakeholders in instituting regulatory policies						
a) Pharmaceutical industry	No	Yes	Yes	Yes	Yes	Yes
b) Researchers/Scientists	No	Yes	Yes	Yes	Yes	Yes
c) Academia	No	Yes	Yes	Yes	Yes	Yes
d) Parliamentarians	No	Yes	Yes	Yes	Yes	Yes
e) Civil Society Organizations (CSOs)	No	Yes	Yes	Yes	Yes	Yes
f) General Public	No	Yes	Yes	Yes	Yes	Yes
Mechanism for stakeholder engagement						
a) Meetings	No	Yes	Yes	Yes	Yes	Yes
b) Workshops	No	Yes	Yes	Yes	Yes	Yes
c) Seminars	No	Yes	Yes	Yes	Yes	Yes
Existence of National Association(s) of Pharmaceutical Industry						
a) Pharmaceutical Manufacturers' Association	No	Yes	No	Yes	Yes	-
b) Pharmaceutical Traders' Association	No	Yes	Yes	Yes	-	Yes
Existence of a mechanism for assessing the level of customer satisfaction with services offered by the NMRA						
a) Client Service Charter	No	Yes	No	Yes	Yes	Yes
b) Customer complaint procedure	No	Yes	No	Yes	Yes	Yes
c) Customer satisfaction surveys	No	Yes	No	Yes	Yes	-

NB: *- = No data available/submitted*

Communication: Communication among the NMRAs in the EAC partner states was evaluated based on the availability of the NMRA's website and availability of important documents in the respective websites as indicated in **Table 3.13**. All NMRAs apart from Burundi reported having websites, moreover, the URLs for the NMRA websites in Kenya, Rwanda, Tanzania, Uganda and Zanzibar were provided and proved to be functional. **Figure 3.10** provides the status of NMRAs websites in the EAC Partner States.

The majority of the NMRAs with functional websites reported to have placed in their websites' documents related to medicines law, regulations, guidelines, fee structure, list of registered products, and a list of licensed establishments (manufacturers, importers, wholesalers/distributors, retailers, others). However, the availability of medicines policy was found to be commonly missing in the Kenya and Uganda NMRA websites.

Other documents indicated to be available in the NMRA websites include safety alerts, application forms, news, events, and frequently asked questions (Tanzania) and application forms, client service charter (Zanzibar).

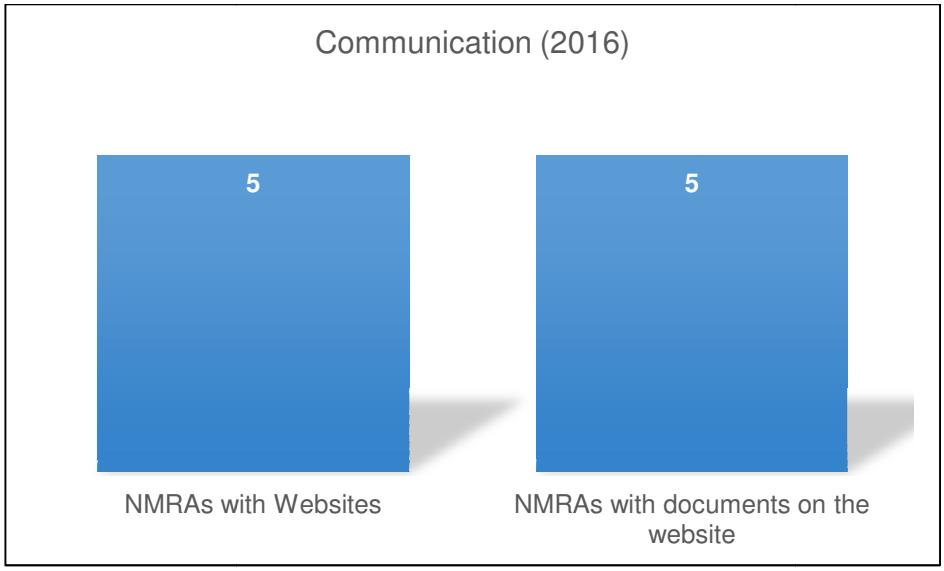

Figure 3.11: Status of NMRAs Websites in the EAC Partner States; 2011/12 – 2015/16.

Table 3. 13 Communication Mechanisms in the EAC Partner States NMRAs; 2011/12 – 2014/15

	National Medicines Regulatory Agency					
Indicator	Burundi	Kenya	Rwanda	Tanzania	Uganda	Zanzibar
Availability of NMRA Website	No	Yes	Yes	Yes	Yes	Yes
If Yes, provide the URL:	NA	www.pharmacyboardkenya.org	www.moh.gov.rw	www.tfda.go.tz	www.nda.or.ug	www.zfdb.go.tz
Availability of documents on the website						
a) Medicines Policy	NA	No	Yes	Yes	No	Yes
b)Medicines Law	NA	Yes	Yes	Yes	No	Yes
c)Regulations	NA	Yes	Yes	Yes	No	Yes
d)Guidelines	NA	Yes	Yes	Yes	Yes	Yes
e)Fees Structure	NA	Yes	No	Yes	Yes	No
f) List of registered products	NA	Yes	Yes	Yes	Yes	No
g)List of rejected products	NA	Yes	No	No	No	No
h)List of banned products	NA	Yes	No	No	No	No
i) List of licensed establishments (manufacturers, importers, wholesales/distributors, retailers, others)	NA	Yes	Yes	Yes	No	No
j) Other documents (specify)	NA	-		Safety alerts, application forms, news, events, FAQs	No	Application forms, Client Service Charter

NB: - = No data available/submitted

3.10 FRAMEWORK FOR MUTUAL RECOGNITION

Chapter 21, Article 18 of the East African Community Treaty among others, stipulates that the partner States harmonize drug registration of pharmaceutical standards without impeding or obstructing the movement of pharmaceutical products within the community [37]. In addition, it urges Partner States to harmonize national health policies and regulations and promote the exchange of information on health issues to achieve quality health within the Community. One of the objectives of the EAC MRH Project was to enable Partner States to recognize each other's regulatory decisions through a framework for mutual recognition. Such a framework would strengthen trust between NMRA's and enhance ownership of drug regulatory processes within the region assuming that all Partner States will be committed to implementing the framework.

A Cooperation Framework Agreement for National Medicines Authorities in the EAC Partner States was endorsed by the EAC Council of Ministers in May 2018 to guide technical collaboration in the regulation of medicines and health technologies [71].

The framework recognises that no NMRA can do everything on its own without interactions, cooperation, and exchange of information with other regulatory authorities if they are to truly protect their citizens and promote public health. The framework considers the progress made under the EAC MRH Project in GMP, Marketing Authorizations, QMS, IMS and harmonization of other regulatory functions such as clinical trials oversight and pharmacovigilance [56].

CHAPTER 4: DISCUSSION, RECOMMENDATIONS AND CONCLUSION

4.1 INTRODUCTION:

This study aimed to evaluate the effect of the EAC MRH Project using a set of key performance indicators to assess NMRAs progress before and after the project was implemented, using the 2010/11 data as baseline. Results of the study show a significant improvement in policy and legal frameworks, NMRA governance and financing, medicines registration and GMP inspection systems, quality management systems, information management systems, human resource capacity for product registration and GMP inspection, level of transparency, and the existing partnerships and coordination mechanisms.

The study has shown that collaboration, harmonization, joint dossier reviews and inspections of manufacturing sites; reliance and cooperation are key factors for building trust and capacity among NMRAs. Results further show that 83.3% of the EAC Partner States have comprehensive medicines laws with autonomous NMRAs. All the NMRAs have functional registration and inspection systems for pharmaceutical manufacturing sites. All NMRAs in the EAC partner states use regional harmonised guidelines for registration, inspection, quality management and information management system with 80% of them attaining ISO:2015 certification. Efficiency of registration processes has improved by 66.6%. Different financing models are used to regulate pharmaceutical markets in the region with Burundi NMRA relying on government funding while others use a combination of government and/or industry fees with minimal donors' contributions.

This chapter has been divided into three main parts namely discussion, recommendations, and conclusion. The discussion part which comprises of 5 sections, aims to interrogate the results, compare with similar initiatives implemented elsewhere and make inference based on the existing literature. Section 4.2.1 of the discussion emphasises on the importance of collaboration among NMRAs, principles behind harmonization of technical requirements for regulation of medical products, the required specialized expertise and scientific rigour to ensure products meet internationally acceptable standards of quality, safety and efficacy. Section 4.2.2

focuses on regulatory governance and financing which is followed by section 4.2.3 on partnerships and coordination of stakeholders. Other discussion topics include accountability and transparency of regulatory processes – section 4.2.4, and the efficiency of regulatory processes – section 4.2.5. Research limitations are explained in section 4.2.6.

4.2 DISCUSSION

In this chapter, findings will be discussed in detail by linking them with the indicators while assessing NMRAs performance. For instance, NMRAs participation in regional and/or global networks to promote convergence and harmonization efforts and expand its collaboration in the regulatory field is an important factor for building capacity and improving performance. In terms of QMS implementation and ISO Certification, it is a demonstration of the NMRAs top management commitment and leadership to develop a culture of continuously improving regulatory services offered to its clients. Continuous improvement to ensure adequacy and effectiveness of QMS is key and can be achieved through different approaches such as management review, customer feedback mechanisms such a customer satisfaction surveys (i.e. internal and external customers and other interested parties). Other indicators such as NMRA financing provide assurance that the Agency will have the resources to perform functions as mandated by the Government.

Given that at the time of baseline survey there was varying degree of automation of regulatory processes with some NMRAs having manual systems, the EAC MRH Project introduced an integrated IMS to support the technical aspects of medicines regulation. The IMS indicators used in this study were meant to capture the level of automation of regulatory services, the efficiency of business processes, the extent at which NMRAs are sharing information among each other and the public at large. The new indicators therefore focused on the functionality of IMS in the NMRAs and EAC Secretariat and attainment of AMRH IMS modules on registration, licencing of premises, import and export, finance management system and its linkage to regulatory functions such as registration, importations, licensing, and inspections. The level of integration of the national with the regional IMS was also crucial for performance assessment.

4.2.1 Regulatory harmonization and collaboration among NMRAs and industry

Assessment of quality, safety and efficacy of medical products requires specialized expertise and scientific rigour to ensure they meet internationally accepted standards [29,72]. Ineffective, poor quality and harmful medicines can result in therapeutic failure, exacerbation of disease, resistance to medicines and sometimes death with subsequent waste of money spent by patients, insurance schemes and governments and ultimately undermining public confidence in health systems [73]. Highly skilled staff, advanced technical equipment and knowledge, effective market monitoring systems, and real decision-making capacity by NMRAs is therefore critical to assure the safety, efficacy and quality of medical products circulating in a particular market [72].

International collaboration amongst NMRAs and harmonization of regulatory requirements are some of the creative and strategic approaches used to strengthen regulatory capacity and assist in making sound decisions [72]. Harmonization of technical requirements for regulation of medical products is a concept mainly driven by trade across countries and has proven to assist in eliminating country-specific scientific reviews, facilitating companies' submission of a single set of dossier to several different countries with subsequent reduction of costs [72]. In addition, harmonization processes contribute to public health promotion through facilitation of open-minded technical discussions and the exchange of ideas and experience among regulators of different countries and subsequently strengthening the capacity of NMRAs [72].

The AMRH initiative works on the principles of collaboration among regulators through harmonization of technical requirements, work sharing, joint assessment of dossiers and inspection of manufacturing sites. This is based on recognition of the value of collaboration and regulatory harmonization as a tool for building trust among participating NMRAs with subsequent improvement in regulatory capacity [19].

Harmonization of legislations, technical requirements for medicines regulation, guidelines and procedures requires effective communication and collaboration as they aim to building capacity and trust among participating NMRAs [75]. Information

sharing, recognition of regulatory decisions and joint working are some of the collaborative approaches used for registration of medical products which would ultimately lead to mutual recognition and/or centralized registration [75].

Divergent medical products regulatory systems and models and desire by the pharmaceutical industry to expand their markets across the globe have necessitated international cooperation among NMRAs and harmonization of pharmaceutical regulations in various forms [76]. For instance, the European Union (EU) first issued a directive related to pharmaceutical products to provide for the definition of a 'medicinal product' and a 'substance' and to set up some fundamental principles for the creation of the European pharmaceutical system in 1965 [77]. The EU Member States adopted standards to ensure a high level of public health protection and the quality, safety and efficacy of authorised medicines through a legal framework governing medicinal products for human use [78]. This aimed to prevent a recurrence of the thalidomide disaster of the late 1950s which affected thousands of babies born with limb deformities due to their mothers taking a medicinal product during pregnancy [78]. In addition, the legal framework aimed to promote the functioning of the internal market and encourage innovation [78].

The European Union [EU]) trade-driven harmonization of regulatory requirements which started in the late 1970s through development of a single body of pharmaceutical legislation and regulations among member countries culminated into establishment of the European Medicines Agency (EMA) in 1995. EMA aimed to harmonize the work of NMRAs in the region, to reduce the cost and eliminate the protectionist tendencies of sovereign states unwilling to approve new drugs that were in competition with domestic markets (at the time, the annual cost for drug approvals by companies stood at €350 million) [79]. Various directives were issued by the EU including requirements for the conduct of clinical trials and legislation against falsified medicines; just to mention a few [78].

Another harmonization scheme, 'The International Cooperation on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)' was established in 1990 bringing together the NMRAs of Europe, Japan and the United States of America (USA) and experts from the pharmaceutical industry in the

three regions [80]. The ICH mission is to promote public health by achieving greater harmonization through the development of technical guidelines and requirements for pharmaceutical product registration and a well established governance structure [80]. To date, over 50 ICH harmonized guidelines have been agreed in the area of quality, safety and efficacy [76]. The ICH has also created a forum that allows experts from different countries and with different backgrounds to communicate, exchange, discuss and share their experiences in a structured manner. Another achievement of ICH is the worldwide recognition of the ICH guidelines with drastic modification of the international cooperation environment [76]. The scientific basis for consensus on technical guidelines reached between the NMRAs and the industry experts and the well-defined structure and processes are key factors attributed to ICH success [76].

In Africa, harmonization and cooperation among NMRAs can be traced back to 1986 when the German Foundation for International Development (DSE) in collaboration with WHO organised a series of meetings and training workshops for drug African regulators to expose them to concepts for drug regulation and harmonization [81]. It wasn't until 1997 when the African Drug Regulatory Authorities Network (AFDRAN) was officially established following the signing of the AFDRAN constitution by nine NMRAs in Harare, Zimbabwe [81]. The last formal AFDRAN meeting was held in 1999, before the International Conference of Drug Regulatory Authorities (ICDRA) held in Berlin, Germany [81]. With limited budgets and piggybacking on other meetings, AFDRAN did not realise its goal to harmonize regulatory standards in Africa [81].

For the Southern African Development Community (SADC) region, pharmaceutical harmonization started in 2004 backed by the SADC Heath Protocol and Health Policy Framework of 1999 and 2000 respectively [76]. The SADC Regulators Forum was subsequently created in 2004 as a technical sub-committee to promote the harmonization and enhancement of pharmaceutical regulations in the region [76]. By 2007, seven (7) technical guidelines on the conduct of clinical trials, registration of medicines, GMP, pharmacovigilance, advertising, and recalls were adopted by member States. Others include guidelines for registration of nutritional supplements, vaccines and traditional medicine; bioavailability and bioequivalence; stability studies

and imports and export control. The Zazibona collaborative collaborative procedure for medicines registration initiated in October 2013 by the four founding member countries namely Zambia, Zimbabwe, Botswana and Namibia has registered significant success since its inception. The scheme which was endorsed by SADC Ministers of Health & Ministers Responsible for HIV & AIDS in January 2015 is now operational across all the countries in the region [83,84]. The objective of the Zazibona agreement is to reduce regulatory workload, accelerate registration of selected products and develop mutual confidence in regulatory collaboration. The agreement also provides a platform for training, harmonization of requirement and practice and collaboration on other regulatory fields [82].

Harmonization of medical products regulation in the EAC region builds on a foundation laid in 1999 following the adoption of the East African Treaty which promotes cooperation amongst Partner States and provided political impetus [85]. Through the AMRH initiative, the EAC Partner States agreed on a set of compendia including guidelines for registration of medicines and GMP inspections. Joint reviews and GMP inspections have been conducted with subsequent shorter registration timelines. Key lessons learnt from the EAC harmonization initiative include the need for clear government policies with robust legal and regulatory frameworks; need for political support with clear long-term objectives and incentives for achieving them such as creating a common market and faster market access. In addition, there is need for effective governance structure, harmonised requirements and standards of practice, and strong commitment from major stakeholders such as regulators and regulated parties. Lessons learnt from EAC MRH Project will assist other regions implementing similar initiatives either on the continent or globally [94-97].

4.2.2 Regulatory Governance and financing

Regulation of medical products demands the application of sound scientific knowledge and specific technical skills and that the NMRA operates within a legal framework [73]. Governments need to establish strong NMRAs to ensure that the manufacture, trade and use of medicines are regulated effectively to protect and promote public health [73].

While globally only 40% of NMRAs operate as autonomous agencies, this research has shown that five out of six (83.3%) NMRAs in the EAC region maintain a certain level of autonomy. While the Republic of Burundi is in the process of establishing an autonomous body, the remaining five (5) NMRAs namely, TMDA, ZFDA, KPPB; Uganda NDA and Rwanda FDA are operating as autonomous agencies.

The increasing level of autonomy provides an opportunity for reduced political interference and increased transparency which is key to ensuring public trust on the performance of the NMRA in a country [47,74]. Advocacy on domestication of the AU Model Law on Medical Products Regulation and the directive to establish Food and Drugs Agencies in the EAC Partner States may be attributed to establishment of autonomous NMRAs. It is also worth noting that the AU Model Law advocates for NMRA's participation in regional and continental harmonization initiatives and promotes regulatory reliance amongst agencies [29].

The AMRH partners' technical, financial, policy and political advocacy support as well as existence of the Steering Committee and EWGs to provide the needed strategic direction and technical advice, have been instrumental in realising the success of the EAC MRH Project.

Sound government policy and legal framework are key factors to empower the NMRA to collect and utilise fees as a means to ensure financial sustainability [47]. Considering that medical products regulation is a public function, safeguarding funding for the regulation of medical products against the competing needs of other government agencies is key for sustainability of NMRAs. In terms of an enabling environment for fees collection by the NMRAs; while the NMRAs in Kenya, Tanzania, Uganda and Zanzibar have legal mandate to collect and utilise fees, Burundi does not.

An alternative funding model is to combine sources from both the government and industry fees, but the collected fees are transferred to the government central treasury as is the case for Malaysia and Venezuela [47]. This is in line with the Sub-Saharan African countries study finding which revealed that 35% of the NMRAs depend on government funding, with all fees paid directly to Treasury [4]. It has also been reported that the fees and charges are set arbitrarily and not necessarily linked to the cost of service provided while resource intensive services are offered free [47].

Another model is where the fees and charges reflect the real cost of services provided such as evaluation of dossiers and inspection of establishments, and the NMRA is financed entirely on fees for service as is the case with the Therapeutic Goods Administration (TGA) in Australia and Medicines Control Authority of Zimbabwe (MCAZ) which have full powers to dispose of the revenue they collect [47]. The TGA Australia is an example of an agency that moved gradually from government-financed to a self-financed agency through a government policy which was phased in over a five years period from 1994-1999 [47].

It is worthwhile noting that one of the limitations in this study is the lack of information on the actual NMRAs fee's structure (which provides different streams of fees charged) and how the funds collected are distributed in performing the different regulatory functions. The limited available data on NMRAs' financing show the main sources of revenue for NMRAs being fees for registration, annual product maintenance, plant audit, premises licensing, import permits, and government subvention and donor funding [24]. In the Southern African Development Community (SADC) region, for instance, the Governments of Lesotho and Namibia fund their NMRAs fully, while in Malawi, Tanzania, Zambia and Zimbabwe, most of the funds are from industry fees [24]. Various sources such as registration and inspection fees as well as imports and retention fees serve as reliable sources of NMRA profits [93]. A further study on fees charged by different NMRAs will provide useful information on fees structure and its basis as well as proportion of contribution from various streams of revenues. The study should also investigate NMRAs funding for participation in regional collaboration and harmonization initiatives as a way to ensure sustainability.

Governments' investment in regional harmonization efforts and strengthening regulatory capacity and systems across NMRAs in the EAC Partner States is key for improving the availability of medicines. For regional initiatives to be sustained, there is a need for NMRAs to set aside a budget for their participation in regional harmonization initiatives.

4.2.3 Partnerships and coordination of stakeholders

Various partners provide either technical, financial, or policy support in the implementation of the EAC MRH Program. Coordination of such support is critical to

ensure effective implementation and cost-effective use of limited resources including alignment of interventions at national and regional levels. While the number of partners providing support in a country may not provide much information, their coordination is critical. It is encouraging to note that in the EAC Partner States; 83% of the countries reported having a mechanism for coordinating the partners including NMRAs in Burundi, Kenya, Rwanda, Tanzania and Uganda.

In as far as regional coordination of partners and stakeholders is concerned; the EAC experience shows that different partners have a comparative advantage in the EAC MRH initiative. While some partners may provide financial support, others have a niche role in providing technical support. In addition, coordination of partners and policy advocacy is another support area that is critical for EAC MRH Project success. What is important is clarity in the roles and responsibilities of the different partners to ensure alignment and avoid duplication of efforts. The EAC Secretariat has a coordination role to ensure the Partner States NMRAs are implementing the project according to plan. From the initial AMRH Partners, the AUDA-NEPAD has a role to provide policy and political advocacy support and coordination of partners and stakeholders involved in the harmonization process. WHO on the other hand has a role to provide the needed technical support in collaboration with Swissmedic. Furthermore, BMGF and DFID provided the initial funding while the World Bank is responsible for providing fiduciary oversight of the GMRH-MDTF.

4.2.4 Accountability and transparency of regulatory processes

Marketing authorization and clinical trials approval have been delayed in the past due to lack of role clarity and lack of transparency between NMRAs and national ethics committees (NECs) [86]. One of the key elements of the EAC MRH Project is to ensure efficient and transparent regulatory processes through the development and implementation of the Common Technical Document (CTD) for registration of medicines; a common IMS and QM; a regulatory capacity building and mutual recognition frameworks as part of the broader AMRH Initiative [19].

There are 5 dimensions to accountability and transparency in regulatory regimes namely, the decision-making process in the setting of rules and standards; the transparency of the rules to be followed; and the activities of the regulated actor.

Other dimensions include; controls exercised on those operating within the set rules; and the feedback process [87]. Regulation is a public good which must seek to balance collective and individual interests while addressing concerns about the transparency and accountability of government actions [88]. Various mechanisms are instituted to ensure accountability of drug regulatory authorities including dissemination of guidelines and other relevant information to the industry and general public through newsletters and websites and/or publication in official gazettes. In addition, regulators are encouraged to maintain regular contacts with the industry to ensure accountability [12].

Transparency is one of the important features observed by the EU regulatory system for medicines, which is about how the system works and how a decision is reached by the NMRA [79]. A typical example is the the European Public Assessment Report (EPAR) which is published for every human or veterinary medicine that has been granted or refused a marketing authorisation following an assessment by EMA. If a medicine is authorised by a member state, details on the assessment of the medicine are also made available in a public assessment report [79]. Investment in regulatory transparency provides value in terms of quality, legitimacy and accountability of regulatory processes [88]. Regulators are therefore encouraged to provide comprehensive and useful annual reports detailing what has been done and achieved over the reporting period and therefore complete the information loop that starts with the corporate and strategic plans [88]. By virtue of their competency and expertise in the policy making process, building on their in-depth technical knowledge of the sector they regulate; regulators are expected to provide transparent advice to government and parliament [89].

For the EAC MRH Project, the integrated IMS for medicines registration in each of the Partner States' NMRAs which is linked between countries and the EAC Secretariat serves as the right strategy for information sharing and communication among NMRAs in the region. A robust IMS is key for supporting the technical aspects of medicines regulation as it facilitates efficiency and effectiveness of business processes, it improves transparency, and decision-making process. The EAC integrated IMS is also key for sharing information between NMRAs and stakeholders and needs to be enhanced to ensure that NMRAs share regulatory

information and publish their assessment reports on their respective websites and the EAC regional platform. This will not only build trust in the regulatory systems in the region but it will also contribute to implementation of mutual recognition procedure, which is the long-term goal of the EAC MRH Project.

The European medicines regulatory system – which is a unique network of around 50 regulatory authorities supported by a pool of thousands of experts drawn from across Europe- serves as a learning platform for EAC [79]. EMA and the Member States cooperate and share expertise in the assessment of new medicines and of new safety information and also rely on each other for the exchange of information in the regulation of medicine, for example regarding the reporting of side effects of medicines, the oversight of clinical trials and the conduct of inspections of medicines' manufacturers and compliance with good clinical practice (GCP), good manufacturing practice (GMP), good distribution practice (GDP), and good pharmacovigilance practice (GVP). Backed by EU legislation, the network also has IT systems which connect all parties and facilitates information exchange on different aspects such as safety monitoring of medicines, authorisation and supervision of clinical trials or compliance with good manufacturing and distribution practices. The European system also provides a marketing authorisation mechanism for products on its market with the object to protect public health and ensure the availability of high quality, safe and effective medicines for European citizens.

4.2.5 The efficiency of regulatory processes

The EAC medicines regulatory harmonization initiative's purpose was to increase access to quality medicines throughout the EAC by harmonizing technical standards and optimizing regulatory requirements and oversight processes for medicines [38]. Through the MRH initiative, the EAC hoped to increase the number of quality medicines it registered by simplifying the application process for manufacturers. It also aimed to increase the speed at which it reviewed applications without decreasing rigor, by modernizing assessment processes and procedures [94-97].

With support from partners including the AU Development Agency–New Partnership for Africa's Development, World Bank, World Health Organization, Swiss Agency for Therapeutic Products (Swissmedic), UK Department for International Development,

and Bill & Melinda Gates Foundation, the initiative provided the needed technical, financial and political advocacy support [94-97]. As a result, countries in the region have developed harmonised regulatory requirements and standards for medical products regulation, dramatically simplifying multistate applications for users and allowing the partner States to begin conducting joint regulatory activities. The initiative has also helped create new NMRAs in Rwanda and Zanzibar. Furthermore, the initiative piloted a process that has reduced the average time it takes for NMRAs to register new medicines by roughly half [94-97].

ISO 9001:2015 certifications by Kenya, Uganda and Zanzibar NMRAs and attainment of WHO GBT Maturity level 3 by TMDA will assure confidence in the quality of work, increasing trust and facilitating reliance on regulatory decisions made and inspections conducted by countries. It is also important to recognise the achievement made by the 3 NMRAs considering that only TMDA was ISO certified when the MRH Project started in 2012 [94-97].

4.2.6 Research limitations

- It is worthwhile noting that one of the limitations in this study is lack of information on the actual NMRAs fees structure for different services provided by NMRAs and how the funds collected are distributed in performing the different regulatory functions. A further study on fees charged by different NMRAs will provide useful information on fees structure and its basis as well as proportion of contribution from various streams of revenues. Inability of the indicator to provide data on funding for NMRAs participation in the EAC MRH Project and the cost for regional coordination is another limitation on financing that needs to be addressed in future evaluations.

- In this study, data on population size, the number of pharmaceutical establishments and the pharmaceutical market size was intended to determine the level of investment (in terms of financial and human resources) required to control the market. However, only Burundi provided data on pharmaceutical market size making analysis and comparison between countries difficult.

- In terms of governance, the study did not provide information on the type of regulations and guidelines currently in force in each country which would have given an indication of robustness of regulatory framework in a country. Furthermore, missing data from some countries and arranging meetings with people and getting national consents was a problem.

- The indicators did not capture the link between the types of products reviewed (Generics, WHO PQ and New active Substances) with the different review timelines and the model employed (full, abridged and verification reviews) as well as any trends over the study period. The indicators on registration systems should be reviewed to link the types of products reviewed, with different review timelines and the model employed as well as any trends over the study period.

- While there is lack of data on the actual regulatory review processes including product category details which would assist in measuring and monitoring regulatory performance at national and regional levels, alignment of the indicators with the CIRS OpERA programme tool will assist in capturing such information.

- Among others, implementation of QMS through documentation of regulatory processes with regular audits to ensure adherence to standard operating procedures and eventual ISO certification may contribute to an NMRA's attainment of WHO Maturity Level III. The indicators can be further refined, and a study conducted to establish the link between the two.

4.3 RECOMMENDATIONS

It should be noted here that data generated from this research is at least 5 years old, stemming from the 2011-2015/2016 study period therefore some of the recommendations may be overtaken by new developments.

4.3.1 Improving efficiency, transparency, and accountability:

IMS and communication platforms are useful tools for building trust among the different stakeholders in the pharmaceutical industry. It is recommended that all

countries in the EAC region should institute transparency and accountability mechanisms to ensure public confidence and trust. This can be done by instituting measures such as posting all the relevant regulatory policies on the website, having a transparent mechanism for engaging stakeholders when instituting new regulatory policies; public education programmes, instituting client service charters and conducting customer satisfaction surveys, just to mention a few.

NMRAs reliance on regulatory decisions made by other agencies; use harmonized guidelines for registration of medicines and GMP inspection, supported by standard operating procedures (SoPs) for a joint review of dossiers and GMP inspection, a harmonized QMS and IMS are necessary tools for increasing efficiency in regulatory processes. Coupled with NMRAs participation in joint review of dossiers for registration medicines and joint inspections; countries are assured of faster approval of medical products.

Given that NMRAs in the EAC region now use harmonized guidelines for registration of medicines and have SoPs for the regional review process, and that all the NMRAs apply QMS principles in their respective countries, it is important that they move to the next level of performance by applying Good Review Practice (GRevP) principles [40]. This will to a large extent ensure that the NMRAs achieve timeliness of the review (i.e. completion within a specified time frame), as well as predictability, consistency, transparency, clarity, efficiency and high-quality review processes which has a significant impact on public health.

It will facilitate patients' access to important medical products, and costs to both government and applicants. GRevPs will further ensure that those involved in the review process have the critical thinking skills and tools needed to optimize scientifically sound, evidence-based decisions and facilitate progress towards regulatory convergence through the exchange of review reports and the enhancement of mutual understanding among NMRAs. Application of project management and quality management principles are critical to well-functioning NMRAs by maximizing the efficiency and effectiveness of the review process. This includes the practice of planning and monitoring review activities coupled with timely, informative communications within the NMRA and clearly-defined work instructions for the reviewers.

4.3.2 Regulatory collaboration and harmonization

Cooperation and collaboration among NMRAs is a critical tool for increasing regulatory capacity especially for NMRAs with limited resources [71]. Exchange of regulatory information, work-sharing among NMRAs and reliance on regulatory decisions made by other agencies is key. No NMRA can do everything alone without interactions, cooperation and exchange of information with other regulatory authorities if they are to truly protect their citizens and promote public health. Progress made under the EAC MRH Project in GMP, Marketing Authorizations, QMS, IMS and harmonization of other regulatory functions such as clinical trials oversight and pharmacovigilance provides a good basis for a successful implementation of the EAC NMRAs Cooperation Framework Agreement.

While EAC MRH reports show reduced timelines for MA from the initial 1-2 years to a 7 months median, concerns raised by the industry as a key stakeholder in the regional harmonization process need to be addressed. This is especially so given the fact that some countries have proven to be faster than others in granting marketing approval of products following regional review process [67]. Many companies are now hesitant to use the joint product assessment procedure until efficiency improvements are made especially for smaller, less attractive markets [67]. Improvements are therefore required to the current EAC processes to meet the vision of harmonization [67]. Companies agree that the regional procedure is of unexpectedly higher quality standards than national procedures [67]. Improved efficiency of the EAC joint review process will attract more applications from industry and serve as source of income for the regional initiative [90].

4.3.3 NMRA Human Resource Capacity

The availability of the requisite number of staff with relevant qualifications, skills and knowledge to perform core regulatory and managerial functions is a critical factor for NMRA performance. Only NMRA's from Kenya, Uganda and Tanzania reported having in place a human resource development plan and frameworks for staff skills audit and competence assessment. Furthermore, an annual training programme for staff was reported to be in place in Tanzania-Mainland and Uganda from 2010 but was absent in Kenya over the entire study period. It is recommended that all NMRAs put in place a human resource development plan, with clear skills audit and

competence assessment framework for staff and annual training programmes coupled with annual staff appraisal mechanisms.

To have an objective analysis of human resource capacity in product assessment and GMP inspections more data is needed to determine not only about the number of staff but also the relevant qualifications, skills and knowledge to perform the assigned duties. In addition, the total number of applications received and GMP inspections planned per year can be used to determine the number of product assessors and GMP inspectors needed per NMRA.

The national and regional training programmes have contributed to building NMRAs capacity in terms of skills and knowledge with subsequent establishment of a pool of experts that have been used as trainers to train other staff in the region under the EAC harmonization program. Further assessment is needed to determine the pool of assessors and GMP inspectors in the region with relevant skills, knowledge and experience to assist and facilitate training programmes using regional centres of regulatory excellence.

There is a need to establish a Competence Development Framework for assessors, GMP inspectors and other regulatory experts as a tool for building necessary knowledge and skills in regulatory science. The approach towards a global competency framework for regulators of medical products can be employed as means to increase a credible regulatory workforce in Africa [91]. In addition, there is a need to establish a clear career development pathway for all regulatory professionals including assessors and GMP inspectors.

4.3.4 Monitoring and evaluations of regional harmonization initiatives

Monitoring and evaluation of NMRAs performance to assess if perceived regulatory objectives have been met, to identify weaknesses and take corrective actions, contribute to the success of a regulatory authority [73]. For instance, in the EU national regulators are required to collaborate in line with respective Community regulations, to collaborate with all stakeholders, ensure transparency and accountability in regulatory decision-making process supported with good management and effective internal quality system [73]. In Africa, the AU Model Law on Medical Products Regulation advocates for NMRAs participation in regional,

continental and international cooperation and harmonization initiatives [29]. In addition, the AU Model Law promotes creation of monitoring and evaluation mechanisms to review and assess performance of NMRAs [29].

Currently, the WHO Global Benchmarking Tool has proven to be a useful tool to objectively assess national regulatory systems [43]. However, there is no tool to determine the value of an investment in NMRAs' participation in regional medicines regulatory harmonization schemes. The development of indicators to assess the various aspects of the EAC MRH Project provides good basis for future evaluations of regional initiatives. Alignment of the national and regional assessment tools will also add value in determining the NMRAs maturity levels and identifying countries that need support.

Currently, the tool has a total of 29 indicators grouped into 9 categories focusing on policy and legal frameworks, NMRA governance, NMRA financing, registration and GMP inspection systems and human resources capacity. Other categories include the contribution of QMS and IMS systems in improving the efficiency and transparency of regulatory processes. While these indicators have assisted in assessing the effect of EAC MRH Project on regulatory capacity in the Partner States NMRAs, they can be further refined to determine the relevance to NMRAs participation in regional harmonization initiatives. For instance, additional indicators on funding for NMRAs participation in regional programmes and a mechanism for funding regional coordination will add value to the existing indicators.

Other mechanisms to support regional initiatives such as partners' contribution and coordination are critical to ensure success and sustainability of regional harmonization schemes. The existence of a mechanism for engaging key stakeholders such as industry and patients in instituting regulatory policies is critical. Communication and sharing of information among NMRAs and with stakeholders and the general public is also a pre-requisite to transparency and accountability of regulatory processes. Maintaining regular contacts between regulatory and the especially when new regulatory policies and technical requirements are instituted instills trust and confidence among the various stakeholders and ensures accountability.

Enforcement of the Cooperation Framework Agreement for National Medicines Authorities in the EAC Partner States is essential for technical collaboration in the regulation of medicines and health technologies to be meaningful. This will enable the EAC Partner States NMRAs to recognize each other's regulatory decisions and eventually achieve the long-term mutual recognition goal. It will also strengthen trust between NMRA's and enhance ownership of drug regulatory processes in line with the East African Community Treaty objectives. Chapter 21, Article 18 of the EAC Treaty clearly stipulates the need for Partner States to harmonize drug registration of pharmaceutical standards without impeding or obstructing the movement of products within the community. The Treaty further urges Partner States to harmonize national health policies and regulations and promote the exchange of information on health issues to achieve quality health within the Community.

4.3.5 Recommendations for future research

Further research areas include a study on the type of regulations and guidelines that are in force in each of the countries which will assist to determine the robustness of countries' regulatory framework.

A study to determine whether QMS improves efficiency of regulatory processes including the actual process of approval of products and the prevailing regulatory systems in respective countries is also another area for exploration. A link between NMRA's ISO certification and attainment of WHO GBT Maturity Level 3 need to be established.

The indicators on registration systems should be reviewed to link the types of products reviewed (Generics, WHO PQ and New active Substances) with the different review timelines and the model employed (full, abridged and verification reviews) as well as any trends over the study period.

In addition, a study on fees charged by different NMRAs will provide useful information on fees structure and its basis as well as proportion of contribution from various streams of revenues. The study should also look into NMRAs funding for participation in regional collaboration and harmonization initiative as a way to ensure sustainability.

4.4 CONCLUSION

The AMRH Initiative aimed to improve the fragmented regulatory system for product registration in Africa by changing from a country-focused approach to a collaborative regional and simplified one [19]. The Initiative initially focused on addressing delays in marketing authorisation with a view to eventually work on an expedited review of clinical trials authorization for vaccines and medicines in Africa [19]. Following the launch of the EAC MRH Project in 2012, there has been significant improvement in registration timelines in EAC and the Southern African Development Community (SADC) member states.

The overarching vision of the EAC's MRH initiative is to increase the number of quality medicines registered in the region by simplifying the application process for manufacturers and increasing the efficiency with which applications were assessed by the partner States. The EAC MRH Project has succeeded in increasing the efficiency with which registration applications for medicines are assessed. With initial focus on harmonization of medicines registration, the EAC MRH Project is poised to expand the scope to other key regulatory functions such as pharmacovigilance, post-market surveillance activities and clinical trials oversight for the AMRH Initiative is to bring full benefits [19]. The EAC Partner States political will to support regional integration as well as willingness of NMRAs to work together coupled with partners' political advocacy, financial and technical assistance are critical success factors.

While currently, the level of products registered through the regional review process is still low, a robust harmonization will lead to an increase in the attractiveness of the EAC regional process and serve as a target market for not only domestic but also international pharmaceutical manufacturers [90]. It is important for EAC MRH Project governance to consider moving towards a regulatory system that is far more targeted and sensitive to the needs of the EAC citizens while setting an example for harmonization across Africa and the globe [90]. A true harmonization will be a win-win for countries, patients, regulatory systems and pharmaceutical companies alike [93].

EAC Partner States NMRAs should embrace the framework for cooperation to facilitate the decision-making process. More efforts are needed to improve capacities

in less-resourced NMRAs such as Burundi, Rwanda and Zanzibar both in human resources and infrastructure and to embrace work sharing, reliance and recognition of other NMRAs regulatory decisions. The NMRAs financing mechanisms also need to be reviewed to ensure appropriate policies and legal frameworks are put in place. Setting realistic fees structure for services offered and retention of funds by NMRAs to perform regulatory activities are key for sustainability. An options analysis for sustainable funding of regional regulatory harmonization programmes needs to be conducted to guide policy on joint assessment of dossiers and GMP inspection of manufacturing sites.

The EAC MRH Project has demonstrated that improving the fragmented regulatory system for product registration by changing from a country-focused to a collaborative regional and simplified approach is possible [19]. The use of regional regulatory platforms to harmonize technical requirements and guidelines for registration of medicines, conducting joint regional dossier assessments, and GMP inspections is working. Critical to this success is work-sharing and pooling of resources with subsequent streamlined decision-making processes at national level.

Policy and legal frameworks, good governance, reliable financing mechanism, harmonized regulatory requirements, standards and practice, coordinated training programmes, IMS and QMS are but some of the factors that can be attributed to EAC success. Others are harmonizing regulatory standards across countries, work and cost-sharing arrangements and collaboration between NMRAs. Advocacy and information campaigns are key for addressing the existing limitations, increasing visibility on the importance of effective regulation of medical products and its contribution to public health and economic development [23].

The political support provided by the EAC Policy Organs, AMRH Partners' commitments to providing the initial funding, technical and policy advocacy support are key for realization of the EAC long-term goals of mutual recognition. In addition, commitment from major stakeholders such as regulators and regulated parties; effective governance structure with authority supported by well-resourced and effective secretariat are also critical factors for success. This coupled with a clear "business model" with processes and procedures clearly defined and followed by

NMRAs, adequate human and financial resources; transparency and effective communication to and with affected stakeholders such as patients, medical community and academia, special interest groups; are necessary factors.

The role of the AMRH initiative and its contribution to increasing regulatory capacity across the continent has been observed. The study further demonstrated the effect of the EAC MRH Project in improving NMRAs capacity in the region and its impact on improving efficiency, transparency, and accountability of regulatory processes. Shared knowledge and skills, and improved capacity amongst participating technical experts from NMRAs in the region are one of the benefits. Others include reduction of duplicative efforts by partners, improved understanding and cooperation among the various stakeholders, and improved work-sharing among NMRAs with subsequent faster regulatory approvals and improved availability to safe, efficacious and quality medicines to the people of the region.

Partnerships are a necessary ingredient to development if they are well managed and coordinated [19]. Identifying various partners supporting the various streams of the EAC MRH Project is necessary. The AMRH Partnership has been established to reduce unnecessary duplication of regulatory systems strengthening and harmonization efforts and maximise utilization of already limited resources [19]. Now that the AMRH Initiative is expanding to cover other regulatory functions and products. alignment of partners' support is critical [19]. AUDA-NEPAD's role in coordinating the AMRH Partnership Platform (AMRH-PP) as the Africa chapter of the Global Coalition of Interested Partners (CIP) under the oversight of the AMRH Steering Committee is necessary [19]. The AMRH initiative also serves as a good foundation for establishment of the African Medicines Agency as a Specialised Agency of the AU [19]. Africa needs strong institutions that can address the challenges of access to quality, safe and efficacious medical products and technologies and sustain the existing interventions largely supported by donors [19]. The AMA will contribute to reducing technical barriers to trade especially at this time when the RECs are rapidly moving towards stronger economic integration such as the EAC Common Market and the Customs Union which have been operational since 2010.

Looking forward, AMRH will continue to work towards improving medicines regulatory and harmonization landscape in Africa in line with its vision of ensuring that African people have access to the needed essential medical products and technologies. Alignment of regulatory systems strengthening and harmonization efforts and advocating for the establishment of AMA is key for optimizing pharmaceutical markets and sustainability in the supply of medical products and technologies for diseases disproportionately affecting Africa. AMA will play a critical role in advancing the AfCFTA including the envisaged pool procurement initiatives for Small Island States and RECs advocated through UNECA pharmaceutical sector project. AMA will also serve as a vehicle for optimising regulatory environment for promotion of local production of pharmaceuticals in Africa, reducing dependence on imports and contributing to the PMPA objective of increasing access to safe, efficacious and good quality medical products to the Africa population.

NMRAs should develop a culture of capturing regulatory information to assist in monitoring and evaluating performance to inform policy decisions by Governments. The indicators generated from this research can be replicated for evaluation of similar initiatives across and beyond the African continent and contribute to public health policy.

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PART II

6. PUBLICATIONS

6.1 DECLARATION OF CONTRIBUTION AND CO-AUTHORS AGREEMENT

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31 May, 2020

Post Graduate Office

Dear Sir/Madam;

Re: DECLARATION OF MARGARETH NDOMONDO-SIGONDA's CONTRIBUTION TO ARTICLES AS PART OF PhD THESIS AND CO-AUTHORS AGREEMENT

I, Margareth Ndomondo-Sigonda, student number 766425, declare that this Thesis Report, titled: "Evaluation of Medicines Regulatory Interventions in the East African Community Region", is composed by myself and that the work has not been submitted for any other degree or professional qualification. I confirm that I contributed adequately towards research findings published in the article(s) stated below which are included in my Thesis Report.

Signature of Student  Date: 05 May 2020

Approved By:

Approved By:
Supervisor 1

Name & Signature: Dr Jacquelin Miot
Health Economics and Epidemiology Research Office, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of Witwatersrand.

Date: 8/5/2020

Supervisor 2

Name & Signature: Prof Shan Naidoo
Public Health Medicine Department, School of Public Health, University of Witwatersrand.

Date: 5/5/2020

Agreement by co-authors:

By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of his/her Thesis/Dissertation/Research Report.

Article 1: Medicines Regulation in Africa: The Current State and Opportunities. Pharmaceutical Medicine. 2017: vol 31(6): 383-397. doi: 10.1007/s40290-017-0210-x. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5691122/

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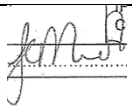
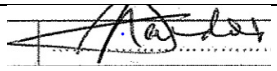
1st Author	Margareth Ndomondo-Sigonda		05 May 2020

2nd Author	Jacquelin Miot		08 May 2020
3rd Author	Shan Naidoo		05 May 2020
4th Authors	Alex Dodoo		31 May 2020
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Article 2: The African Medicines Regulatory Harmonization Initiative: Progress to Date; Medical Research Archive; Feb. 2018. MRA, [S.l.], v. 6, n. 2, ISSN 2375-1924. doi.org/10.18103/mra.v6i2.1668. Available at: https:// https://journals.ke-i.org/index.php/mra/article/view/1668

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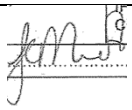
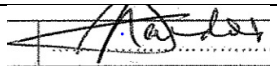
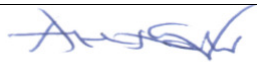
1st Author	Margareth Ndomondo-Sigonda		05 May 2020
2nd Author	Jacquelin Miot		08 May 2020
3rd Author	Shan Naidoo		05 May 2020
4th Authors	Aggrey Ambali		31 May 2020
5th Author	Alex Dodoo		31 May 2020
6th Author	Hlazo Mkandawire		31 May 2020

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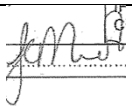
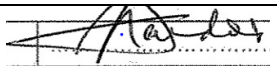
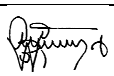
Authors	Name	Signature	Date
1st Author	Margareth Ndomondo-Sigonda		05 May 2020
2nd Author	Jacquelin Miot		08 May 2020
3rd Author	Shan Naidoo		05 May 2020

4th Author	Brian Ng'andu		31 May 2020
5th Author	Nancy Ngum		31 May 2020
6th Author	Nelson E. Masota		31 May 2020
7th Authors	Eliangiringa Kaale		31 May 2020

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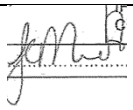
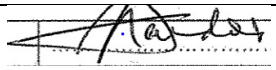
Authors	**Name**	**Signature**	**Date**
1st Author	Margareth Ndomondo-Sigonda		20 June 2020
2nd Author	Jacquelin Miot		20 June 2020
3rd Author	Shan Naidoo		20 June 2020
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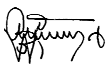
5th Author	Brian Ng'andu		20 June 2020
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CURRENT OPINION

Medicines Regulation in Africa: Current State and Opportunities

Margareth Ndomondo-Sigonda[1,2] · Jacqueline Miot[1] · Shan Naidoo[3] · Alexander Dodoo[4] · Eliangiringa Kaale[5]

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Abstract Sound regulatory systems are critical for protecting public health against use of medical products which do not meet international standards of quality, safety and efficacy. This review provides a summary of the current status of National Medicines Regulatory Authorities (NMRAs) in Africa, and various initiatives that have been established to improve their performance. All countries in Africa (except Sahrawi Republic), have NMRAs but their organizational set-up and functionality is variable. Some are located within Ministries of Health and others are semi-autonomous. There is progressive improvement in regulatory capacity, particularly in quality control and post-marketing surveillance, pharmacovigilance and clinical trials oversight. The African Vaccines Regulatory Forum, African Medicines Regulatory Harmonization Initiative, Network of Official Medicines Control Laboratories and WHO Prequalification Scheme have helped countries strengthen their regulatory capacities. The potential establishment of the African Medicines Agency (AMA) in 2018 is an opportunity to improve NMRAs' capacity in Africa.

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Key Points

All African countries, except one, have National Medicines Regulatory Authorities

No national medicine regulatory authority in Africa can undertake the full range of regulatory functions

The proposed African Medicines Agency provides an opportunity for harmonizing and strengthening NMRAs in Africa

1 Introduction

Medical products, including medicines (drugs), vaccines, blood products, diagnostics and medical devices are critically important for healthcare delivery in all countries. Every country needs an assured supply of safe, efficacious, good quality and affordable medical products to promote public health and patient care [1]. Sound and effective regulatory systems are needed to ensure the quality, safety and efficacy of medical products and for promotion of trade and socioeconomic advancement [2]. Medical products are highly regulated due to the critical role they play in society and the complexities, and sometimes controversies, associated with assessing their safety, quality, efficacy and effectiveness [3]. All countries therefore need to have effective and efficient National Medicines Regulatory Agencies (NMRAs).

Globally, the World Health Organization (WHO) estimates that at least 30% of NMRAs have limited capacity to perform the core regulatory functions [1]. According to WHO, there are 54 NMRAs in Africa, but

their capacity is variable with most of them incapable of performing the core functions expected of NMRAs [1]. The WHO report shows that only 7% of African countries have moderately developed capacity with more than 90% having minimal or no capacity [4]. The absence of functional NMRAs in any country (i) exposes the population to potentially unsafe medical products of variable quality and effectiveness; (ii) facilitates the proliferation of substandard, spurious, falsely labelled, falsified and counterfeit (SSFFC) medical products; and (iii) prevents rational use of medical products, all of which are detrimental to public health and patient safety [5, 6].

Historically, NMRAs were first established in Britain (1880s), Switzerland (1900), USA (1906), Norway (1928) and Sweden (1934) mainly for patent protection and trade promotion, though the laws in Norway and Sweden focused on product safety as well [7]. In the USA, the death of 100 people after intake of sulphanilamide elixir prompted legislation (Pure Food and Drugs Act, 1938) to be passed that required assessment of safety before any product is sold. In the early 1960s, the thousands of pregnancies affected by thalidomide-induced phocomelia and other defects served to transform drug safety and drive the establishment of NMRAs globally [8].

This led to action from the WHO and its member states that called for rigorous testing of medicines during development and after their release for general use [9]. Currently, no medical products are permitted to be sold in any country unless these products have been approved by the respective NMRAs. The absence of well-resourced and functional NMRAs, therefore, has the effect of restricting access to life-saving commodities [10].

Understanding the current state of NMRAs in Africa provides a basis for identifying gaps and existing opportunities for improving regulatory capacity, promoting public health and advancement of pharmaceutical industry. This manuscript draws upon original research, published reports and data from the New Partnership for African Development (NEPAD) Agency and the WHO, including the WHO Pharmaceutical Sector Profiles and Country Reports [11], as well as policy statements and documentation, to provide an overarching summary of NMRAs in Africa. It also discusses opportunities for strengthening NMRAs' performance, including the role of the African Vaccines Regulatory Forum (AVAREF), Network of Official Medicines Control Laboratories (NOMCOL), African Medicines Regulatory Harmonization (AMRH) Initiative, and others that are aimed to improve the regulation of medical products in Africa.

2 Current State of Medicines Regulatory Systems in Africa

Effective regulation of medical products requires a comprehensive legal basis with appropriate and adequate governance mechanisms; sound technical expertise and scientific tools; sustainable funding; coordination of regulatory activities; and monitoring and evaluation to assess performance [6, 12]. The legal basis gives the NMRA power to perform a function while the level of autonomy in executing its mandate, the appropriate structure that allows for proper coordination of various regulatory activities, availability of financial resources and adequate number of human resources with requisite competency to carry out their duties are prerequisites to its performance [13]. The core NMRA functions include: marketing authorization (MA); licensing of manufacturing establishments; imports and export control; inspection of manufacturing premises and distribution channels; market surveillance (product quality monitoring, pharmacovigilance, control of drug promotion and advertising); quality control; and oversight of clinical trials on drugs [12].

This paper focuses on policy and legal basis for regulation; organisational set-up; management systems; financing mechanisms; human resources and performance of core NMRA functions.

2.1 NMRAs Organizational Setup, Financing and Management System

According to WHO, there are 54 NMRAs in Africa [1]. All countries in Africa except the Sahrawi Republic have an NMRA or an administrative unit carrying out some or all tasks expected of NMRAs as shown in Table 1. One country—United Republic of Tanzania—has two NMRAs, namely the Tanzania Food and Drugs Authority and the Zanzibar Food and Drugs Board. While NMRAs in Africa have varying degrees of maturity, their organisational structures, remits and activities also vary widely, some being semi-autonomous whilst others operate within the Ministry of Health (MoH). Some regulate only medical products, whilst others regulate food and cosmetics as well. All NMRAs eventually report to the MoH with the Minister of Health having overall responsibility.

The limited available data on NMRAs' financing show the main sources of revenue for NMRAs are fees for registration, annual product maintenance, plant audit, premises licensing, import permits, and government subvention and donor funding. A study on the East African Community (EAC) NMRAs shows that the Tanzania Food and Drugs Authority (TFDA), Kenya Pharmacy and Poisons Board (KPPB) and National Drug Authority (NDA) of Uganda

Table 1 Organisational set-up and functions performed by NMRAs in Africa Source: Various Reports, Websites; including national government websites, WHO websites, African Union websites, and general web resources *U* information not available

Country	Organisational set up	Product Assessment & registration	Licencing manufacturers	Licencing wholesalers, distributors	Imports and exports control	Inspection of manufacturing establishments	Inspection of distribution channels/Outlets	Quality control laboratory
Algeria	Direction de la Pharmacie et du Médicament. Ministère de la Santé, de la Population et de la Réforme Hospitalière; MoH	U	U	U	U	U	U	✔
Angola	Direcao Nacional de Medicamentos e Equipmentos, Ministerio de Saude; MoH	✔	✔	✔	✔	✔	✔	U
Benin	Direction de la Pharmacie et des explorations diagnostics; MoH	U	U	U	U	U	U	U
Botswana	Drug Regulatory Services, Ministry of Health and Wellness; MoH	✔	✔	✔	✔	✔	✔	✔
Burkina Faso	Direction Générale de la Pharmacie, du Médicament et des Laboratoires; Semi-Autonomous	✔	✔	✔	✔	✔	✔	✔
Burundi	Direction de la pharmacie, du Meicament et des Laboratories; MoH	✔	✔	✔	✔	U	U	✔
Cabo Verde	Agência de Regulação e Supervisão dos Produtos Farmacêuticos e Alimentares; MoH	U	✔	U	✔	U	U	U
Cameroon	Direction de la Pharmacie, du Médicament et des Laboratoires; MoH	U	U	U	U	U	U	U
Central African Republic	Direction des services Pharmaceutiques des laboratoires et de la Médecine Traditionnelle, Ministère de la Santé publique et de la Population; MoH	U	U	U	U	U	U	U
Chad	Direction Générale de la Pharmacie et Laboratoire, Ministère de la Santé Publique; MoH	U	U	✔	✔	U	U	U
Comoros	Direction des Laboratoires et des Pharmacies; MoH	U	U	U	U	U	U	U
Congo	Direction des Pharmacies, du Médicament et des Laboratoires. Ministère de la Santé Publique et des Affairs Sociales; MoH	U	U	U	U	U	U	U
Côte d'Ivoire	Direction de la Pharmacie et du Médicament. Ministre de la Sante et de l'Hygiene Publique; MoH	✔	✔	✔	✔	✔	✔	✔
DR Congo	Direction de la Pharmacie et du Médicament. Ministère de la Santé Publique; MoH	✔	✔	✔	✔	✔	✔	✔
Djibouti	Direction du Médicament et de la Pharmacie, Ministère de la Santé; MoH	U	U	U	U	U	U	U

Table 1 continued

Country	Organisational set up	Product Assessment & registration	Licencing manufacturers	Licencing wholesalers, distributors	Imports and exports control	Inspection of manufacturing establishments	Inspection of distribution channels/Outlets	Quality control laboratory
Egypt	Egyptian Drug Authority; MoH	U	U	U	U	U	U	✔
Equatorial Guinea	Direction Générale de Pharmacie et Médecine Traditionnelle; MoH	U	U	✔	✔	U	U	U
Eritrea	National Medicine and Food Administration; MoH	U	U	U	U	U	U	U
Ethiopia	Food, Medicine and Health Care Administration and Control of Ethiopia; Semi-Autonomous	✔	✔	✔	✔	✔	✔	✔
Gabon	Direction Médicament et de la Pharmacie; MoH	U	U	U	U	U	U	U
Gambia	Newly established Medicines Control Agency; MoH	U	✔	U	U	U	U	U
Ghana	Food and Drugs Authority; Semi-Autonomous	✔	✔	✔	✔	✔	✔	✔
Republic of Guinea	Direction Nationale de la Pharmacie et du Laboratoire; MoH	U	✔	U	✔	U	U	U
Guinea Bissau	Direction de services Pharmaceutiques, de Laboratoire et du Médicament; MoH	U	U	U	✔	U	U	U
Kenya	Pharmacy and Poisons Board; Semi-Autonomous	✔	✔	✔	✔	✔	✔	✔
Lesotho	Ministry of Health; MoH	U	U	U	U	U	U	U
Liberia	Liberia Medicines and Health Products Regulatory Authority; MoH	U	✔	U	U	U	U	✔
Libya	Pharmacy Management Department, Ministry of Health; MoH	U	U	U	U	U	U	U
Madagascar	Direction de la Phamacie, des Laboratoires et de la Médecine Traditionnelle; MoH	U	✔	✔	✔	✔	✔	✔
Malawi	Pharmacy, Medicines and Poisons Board; MoH	✔	✔	✔	✔	✔	✔	✔
Mali	Direction de la Pharmacie et des Médicaments, Ministre de la Sante et de l'Hygiene Publique; MoH	U	✔	U	U	U	U	✔
Mauritania	Direction de la Pharmacie et du Médicament Ministère de la Santé Publique et des Affaires Sociales; MoH	U	U	U	U	U	U	U
Mauritius	Pharmacy Board, Ministry of Health and Quality of Life; MoH	✔	✔	✔	✔	✔	✔	✔
Morocco	Direction du Médicament et de la Pharmacie; Semi-Autonomous	✔	✔	✔	✔	✔	✔	✔
Mozambique	Departamento Farmacêutico, Ministério da Saúde; MoH	✔	✔	✔	✔	✔	✔	✔
Namibia	Namibia Medicines Regulatory Council; MoH	✔	✔	✔	✔	✔	✔	✔

Table 1 continued

Country	Organisational set up	Product Assessment & registration	Licencing manufacturers	Licencing wholesalers, distributors	Imports and exports control	Inspection of manufacturing establishments	Inspection of distribution channels/Outlets	Quality control laboratory
Niger	Direction de la Pharmacie, des Laboratoires et de la Pharmacopée Traditionnelle, Ministere de la Sante Publique; MoH	U	✔	U	✔	U	U	U
Nigeria	National Agency for Food and Drug Administration and Control; MoH	✔	✔	✔	✔	✔	✔	✔
Rwanda	Department of Pharmaceutical Services, Ministry of Health; MoH	✔	U	✔	✔	✔	✔	✔
Sahrawi Republic	No NMRA identified	U	U	U	U	U	U	U
São Tomé and Príncipe	Direction de la Pharmacie et du Médicament Ministère de la Santé; MoH	U	U	U	U	U	U	U
Senegal	Direction de la Pharmacie et du Médicament, Ministère de la Santé et de l'Action sociale; MoH	U	✔	✔	✔	✔	✔	✔
Seychelles	Medicines Regulation Unit, Public Health Authority, Ministry of Health; MoH	U	U	U	U	U	U	U
Sierra Leone	Pharmacy Board of Sierra Leone; Semi-Autonomous	✔	✔	✔	✔	✔	✔	✔
Somalia	Pharmaceutical and Medical Department, Ministry of Health; MoH	U	U	U	U	U	U	U
South Africa	Medicines Control Council; Semi-Autonomous	✔	✔	✔	✔	✔	✔	✔
South Sudan	Food and Drugs Control Authority, South Sudan; Semi-Autonomous	U	U	U	U	U	U	U
Sudan	National Medicines and Poisons Board; Semi-Autonomous	✔	✔	✔	✔	✔	✔	✔
Swaziland	Pharmaceutical Services Department, Ministry of Health; MoH	✔	✔	✔	✔	U	U	U
Togo	Direction des Pharmacies, des Laboratoires et des Equipements Technique, MINISTRE DE LA SANTE ET DE LA PROTECTION SOCIALE; MoH	U	✔	U	✔	U	U	U
Tunisia	Direction de la Pharmacie et du Médicament; Semi-Autonomous	U	✔	U	U	U	U	✔
Uganda	National Drugs Authority; Semi-Autonomous	✔	✔	✔	✔	✔	✔	✔
UR of Tanzania	1. Tanzania Food and Drugs Authority; Semi-Autonomous	✔	✔	✔	✔	✔	✔	✔
	2. Zanzibar Food, Drugs and Cosmetics Board; Semi-Autonomous	✔	✔	✔	✔	✔	✔	✔

Table 1 continued

Country	Organisational set up	Product Assessment & registration	Licencing manufacturers	Licencing wholesalers, distributors	Imports and exports control	Inspection of manufacturing establishments	Inspection of distribution channels/Outlets	Quality control laboratory
Zambia	Zambia Medicines Regulatory Agency; Semi-Autonomous	✔	✔	✔	✔	✔	✔	✔
Zimbabwe	Medicines Control Agency Zimbabwe; Semi-Autonomous	✔	✔	✔	✔	✔	✔	✔

Country	Organisational set up	Market surveillance	Safety surveillance	Control of drug promotion & advertisement	Control of clinical trials	International cooperation & harmonization	Quality management systems
Algeria	Direction de la Pharmacie et du Médicament. Ministère de la Santé, de la Population et de la Réforme Hospitalière; MoH	U	U	U	U	U	U
Angola	Direcao Nacional de Medicamentos e Equipmentos, Ministerio de Saude; MoH	U	U	U	U	U	U
Benin	Direction de la Pharmacie et des explorations diagnostics; MoH	U	U	U	U	U	✔
Botswana	Drug Regulatory Services, Ministry of Health and Wellness; MoH	✔	U	U	U	U	✔
Burkina Faso	Direction Générale de la Pharmacie, du Médicament et des Laboratoires; Semi-Autonomous	✔	✔	✔	✔	✔	✔
Burundi	Direction de la pharmacie, du Meicament et des Laboratories; MoH	U	U	U	U	U	✔
Cabo Verde	Agência de Regulação e Supervisão dos Produtos Farmacêuticos e Alimentares; MoH	U	✔	✔	✔	U	✔
Cameroon	Direction de la Pharmacie, du Médicament et des Laboratoires; MoH	U	U	U	U	U	U
Central African Republic	Direction des services Pharmaceutiques des laboratoires et de la Médecine Traditionnelle, Ministère de la Santé publique et de la Population; MoH	U	U	U	U	U	U
Chad	Direction Générale de la Pharmacie et Laboratoire, Ministère de la Santé Publique; MoH	U	U	U	U	U	U
Comoros	Direction des Laboratoires et des Pharmacies; MoH	U	U	U	U	U	U
Congo	Direction des Pharmacies, du Médicament et des Laboratoires. Ministère de la Santé Publique et des Affairs Sociales; MoH	U	U	U	U	U	U

Table 1 continued

Country	Organisational set up	Market surveillance	Safety surveillance	Control of drug promotion & advertisement	Control of clinical trials	International cooperation & harmonization	Quality management systems
Côte d'Ivoire	Direction de la Pharmacie et du Médicament. Ministre de la Sante et de l'Hygiene Publique; MoH	✔	✔	✔	✔	✔	✔
DR Congo	Direction de la Pharmacie et du Médicament. Ministère de la Santé Publique; MoH	U	U	U	U	U	U
Djibouti	Direction du Médicament et de la Pharmacie, Ministère de la Santé; MoH	U	U	U	U	U	U
Egypt	Egyptian Drug Authority; MoH	U	U	U	U	U	U
Equatorial Guinea	Direction Générale de Pharmacie et Médecine Traditionnelle; MoH	U	U	U	U	U	U
Eritrea	National Medicine and Food Administration; MoH	U	U	U	U	U	U
Ethiopia	Food, Medicine and Health Care Administration and Control of Ethiopia; Semi-Autonomous	✔	✔	✔	✔	✔	✔
Gabon	Direction Médicament et de la Pharmacie; MoH	U	U	U	U	✔	U
Gambia	Newly established Medicines Control Agency; MoH	U	✔	U	U	✔	U
Ghana	Food and Drugs Authority; Semi-Autonomous	✔	✔	✔	✔	✔	U
Republic of Guinea	Direction Nationale de la Pharmacie et du Laboratoire; MoH	U	✔	✔	U	✔	U
Guinea Bissau	Direction de services Pharmaceutiques, de Laboratoire et du Médicament; MoH	U	✔	✔	U	✔	U
Kenya	Pharmacy and Poisons Board; Semi-Autonomous	✔	✔	✔	✔	✔	✔
Lesotho	Ministry of Health; MoH	U	U	U	U	✔	U
Liberia	Liberia Medicines and Health Products Regulatory Authority; MoH	U	✔	✔	✔	✔	U
Libya	Pharmacy Management Department, Ministry of Health; MoH	U	U	U	U	U	U
Madagascar	Direction de la Phamacie, des Laboratoires et de la Médecine Traditionnelle; MoH	U	U	U	U	✔	U
Malawi	Pharmacy, Medicines and Poisons Board; MoH	U	U	U	U	✔	
Mali	Direction de la Pharmacie et des Médicaments, Ministre de la Sante et de l'Hygiene Publique; MoH	U	✔	✔	✔	✔	U
Mauritania	Direction de la Pharmacie et du Médicament Ministère de la Santé Publique et des Affaires Sociales; MoH	U	U	U	U	U	U

Table 1 continued

Country	Organisational set up	Market surveillance	Safety surveillance	Control of drug promotion & advertisement	Control of clinical trials	International cooperation & harmonization	Quality management systems
Mauritius	Pharmacy Board, Ministry of Health and Quality of Life; MoH	U	U	U	U	✔	U
Morocco	Direction du Médicament et de la Pharmacie; Semi-Autonomous	✔	✔	U	U	U	U
Mozambique	Departamento Farmacêutico, Ministério da Saúde; MoH	U	U	U	U	✔	U
Namibia	Namibia Medicines Regulatory Council; MoH	U	U	U	U	✔	U
Niger	Direction de la Pharmacie, des Laboratoires et de la Pharmacopée Traditionnelle, Ministere de la Sante Publique; MoH	U	✔	U	✔	✔	U
Nigeria	National Agency for Food and Drug Administration and Control; MoH	✔	✔	U	✔	✔	U
Rwanda	Department of Pharmaceutical Services, Ministry of Health; MoH	U	U	U	U	✔	✔
Sahrawi Republic	No NMRA identified	U	U	U	U	U	U
São Tomé and Príncipe	Direction de la Pharmacie et du Médicament Ministère de la Santé; MoH	U	U	U	U	✔	U
Senegal	Direction de la Pharmacie et du Médicament, Ministère de la Santé et de l'Action sociale; MoH	U	U	✔	✔	✔	U
Seychelles	Medicines Regulation Unit, Public Health Authority, Ministry of Health; MoH	U	U	U	U	✔	U
Sierra Leone	Pharmacy Board of Sierra Leone; Semi-Autonomous	✔	U	U	U	✔	U
Somalia	Pharmaceutical and Medical Department, Ministry of Health; MoH	U	U	U	U	✔	U
South Africa	Medicines Control Council; Semi-Autonomous	✔	✔	✔	✔	✔	U
South Sudan	Food and Drugs Control Authority, South Sudan; Semi-Autonomous	U	U	U	U	✔	U
Sudan	National Medicines and Poisons Board; Semi-Autonomous	✔	✔	U	U	✔	U
Swaziland	Pharmaceutical Services Department, Ministry of Health; MoH	U	U	U	U	✔	U

Table 1 continued

Country	Organisational set up	Market surveillance	Safety surveillance	Control of drug promotion & advertisement	Control of clinical trials	International cooperation & harmonization	Quality management systems
Togo	Direction des Pharmacies, des Laboratoires et des Equipements Technique, MINISTRE DE LA SANTE ET DE LA PROTECTION SOCIALE; MoH	U	↘	↘	↘	↘	U
Tunisia	Direction de la Pharmacie et du Médicament; Semi-Autonomous	U	U	U	U	U	U
Uganda	National Drugs Authority; Semi-Autonomous	↘	↘	↘	↘	↘	↘
UR of Tanzania	1. Tanzania Food and Drugs Authority; Semi-Autonomous	↘	↘	↘	↘	↘	↘
	2. Zanzibar Food, Drugs and Cosmetics Board; Semi-Autonomous	↘	↘	U	U	↘	↘
Zambia	Zambia Medicines Regulatory Agency; Semi-Autonomous	↘	↘	↘	↘	↘	U
Zimbabwe	Medicines Control Agency Zimbabwe; Semi-Autonomous	↘	↘	↘	↘	↘	↘

charge fees for regulatory work and receive minimal or no government subvention, while in Zanzibar, Rwanda and Burundi, governments fully fund regulatory work [14]. Similarly, in the Southern African Development Community (SADC) region, the Governments of Lesotho and Namibia fund their NMRAs fully, while in Malawi, Tanzania, Zambia and Zimbabwe, most of the funds are from industry fees. Of 26 countries included in a study, 35% of the NMRAs depended on government funding, with all fees paid directly to Treasury, whereas 15% of NMRAs received donor funding, with most countries charging fees for initial MA of products, renewal and retention. Fees for importation of products were rarely charged [12]. More research is needed to determine the various funding models for NMRAs in Africa and mechanisms that will ensure sustainability.

Looking at human resources for NMRAs, reports indicate a general lack of qualified assessors and inspectors [12]. A study conducted in Angola revealed critical understaffing in the Department of Pharmaceutical Inspection (DIF), with a total of 33 staff members at central level, 2 inspectors per province and 1 inspector per municipality [15]. In the EAC countries, there is a general human resource constraint of staff to assess applications and issue licences [16]. Inadequate and unsustainable availability of human resource is a problem affecting most developing countries and is largely caused by low salaries, scarcity of pharmaceutical and other essential professionals, shortage of training institutions, inflexible recruitment procedures, lack of career structure and incentives, and the 'brain drain' [17].

While it is generally agreed that most NMRAs in Africa lack qualified experts to perform critical regulatory functions, the existing literature focuses largely on availability of human resource development plans, job descriptions and responsibilities of key personnel [12]. Literature is sparse when it comes to recording actual numbers of those employed and the requisite expertise and competencies matched to various regulatory functions. Quantifying the existing regulatory expertise in Africa is important, especially given the enormous investment by governments and development partners in training of regulatory experts.

2.2 Policy and Medical Products Regulatory Framework

National Medicines Policies (NMPs) are overarching government commitments to ensure access, quality, and rational use of drugs in a country including a statement on regulation of medicines [18]. Most African countries have NMPs which support regulation of medical products. For instance, review of NMP frameworks in the SADC region shows that, with the exception of Seychelles, most of the

medicine laws in the region are backed by NMPs [19]. In the Central African region, Angola, Chad, Equatorial Guinea and the Democratic Republic of Congo have NMPs in place, whilst in the Economic Community of West African States (ECOWAS) region Burkina Faso, Cape Verde, the Gambia, Ghana, Liberia, Niger, Nigeria, Republic of Guinea, Senegal and Togo have NMPs [14].

Medicines Laws form the foundation for regulation and they need to be comprehensive, covering all areas of pharmaceutical sector activities and a broad range of medical products, and provide adequate powers to the NMRA to control and regulate the pharmaceutical market [13]. A situational analysis of NMRAs in WHO-AFRO region shows that 40 out of 46 of the countries have legislation for medical products, though only 7 (15%) of the NMRAs are legally mandated to perform all five critical regulatory functions [12]. A study conducted in the EAC Partner States revealed some commonalities and disparities of laws with varying degree of implementation and capacity [20]. In the SADC region, all 15 countries have medicines laws with varying degree of comprehensiveness, scope of regulated products, and functions [19]. For the ECOWAS region, 11 countries have medicines laws in place with similar variations, as with the SADC and EAC regions [14].

While WHO recommends that all types of medicines be regulated by NMRAs, there is wide variation across countries in Africa. Of 26 NMRAs, 65% have a mandate to control veterinary medicines; 69% had provisions for regulation of traditional or herbal medicines; 65% regulate a wide range of products including foods, pesticides, poisons, bottled water, cosmetics and/or animal food supplements; and only 15% are mandated to perform all regulatory functions [12]. The differences in legal provisions of key regulatory functions and practices have potentially delayed availability of important medicines in some markets; hence, the need for convergence towards a common medicines regulatory framework which will also facilitate benchmarking among countries in Africa.

2.3 NMRAs Performance of Core Regulatory Functions

Marketing authorisation (MA) Available literature on MA shows that the time it takes for the applicant to be granted MA affects availability of the product on the market. A typical lag of 4–7 years has been recorded between first regulatory submission to a well-resourced NMRA and final approval in sub-Saharan Africa [21]. Lengthy registration times is one of the reasons why companies refuse to supply medicines to certain African countries [22]. Studies also show that the growing demand to assess novel neglected-disease products for African use have necessitated the establishment of various regulatory pathways to facilitate approval including the European Medicines Agency (EMA) Article 58; the WHO Prequalification Scheme; and the United States Food and Drug Administration (US-FDA) Tentative Approval [23]. The performance of MA systems in Africa needs further research, as do licensing, import and export control systems. The available literature on the latter, conducted in Angola, indicates that licensing of pharmaceutical establishments is only granted for retail outlets, leaving the remaining supply chain unattended [24]. While the situation may not be very different in most African countries, more research is needed to determine the performance of NMRAs across the continent in this area.

Pharmacovigilance An assessment of pharmacovigilance (PV) systems in 26 sub-Saharan African countries showed that only 8 (30%) countries collected reports on adverse events with only 3 programmes being sufficiently established to contribute a sizeable number of reports. Of the eight countries collecting adverse events, seven were members of the WHO Programme for International Drug Monitoring (PIDM), and in those countries where a PV system existed, it was not well integrated with other regulatory activities [12]. Membership to the WHO-PIDM is one of the criteria used to determine the performance of PV systems in a country [24, 25]. Membership requires a designated national PV centre, a spontaneous adverse drug reaction (ADR) reporting system, and demonstration of technical competence in managing individual case safety reports (ICSRs) by submitting at least 20 reports to the WHO ICSR database, VigiBase™ [26]. The number of countries that are full members of WHO-PIDM increased from five in 2000 to 35 countries in 2015 with South Africa, Morocco, Nigeria, Egypt and Kenya classified as the main ICSR reporting countries [26]. A further review of specific features of PV in Africa shows that, while the health systems are weak and lacking in basic infrastructure, personnel, equipment and facilities, they have been deploying millions of doses of medicines and vaccines to address diseases of public health importance [25], which calls for a robust PV system.

Post-Marketing Surveillance Post-marketing surveillance (PMS) activities in a country comprise an elaborate framework which includes: review of authorised products; random audits of notified variations; good manufacturing practice (GMP) inspections of local manufacturers; laboratory testing of samples either selected randomly or suspected of being substandard; monitoring of adverse drug reactions; monitoring of advertising and other promotional activities; and drug utilization studies, to mention a few [27]. The importance of PMS activities in the region is easily demonstrated: PMS of antimalarial medicines in Malawi indicated an 88.4% failure rate of samples tested, suggesting the presence of substandard products in the

market and the need for intervention and regular monitoring to ensure delivery of quality health care [28]. In Kenya, a survey of antiretroviral medicines revealed that, while samples analysed conformed to quality standards, one-third of the products found in the market were not registered [29]. A survey of quality of antimalarial drugs circulating in Cameroon, Ethiopia, Ghana, Kenya, Nigeria and the United Republic of Tanzania indicated that 14% of collected samples were not registered by the respective NMRA and the overall failure rates of samples tested were 37, 0, 39, 5, 64 and 11%, respectively [30]. In the case of vaccines, strong partnerships and collaboration between different stakeholders is needed to assure that vaccines are effective and safe when translated in real-world settings [31].

A low rate of post-marketing withdrawal of harmful medicinal products due to adverse drug reactions is attributed to regulatory capacity limitation by most African countries [32]. According to the WHO rapid alert system, there is increasing circulation of substandard and falsified (SSFF) medical products in the African Region and surveys show quality failure rates of up to 28% in some cases [33].

Quality Control Quality control aims to verify that products comply with specifications of MA and testing of post-marketing samples serves as a deterrent against negligent or fraudulent manufacturing and trading practice [13]. NMRAs' access to well-resourced quality control laboratories, which operate according to established standards and organisational frameworks, is key for quality surveillance of products circulating in the market [12]. The Quality Management System (QMS) ISO 17025 and the WHO Guidance on Good Laboratory Practice [34–36] are global benchmarking tools for measuring standards for QC laboratory performance. Achieving either WHO Prequalification or ISO 17,025 accreditation status ensures that a laboratory has demonstrated technical competence to produce precise and accurate data, and that it meets internationally accepted standards of quality and reliability [37].

Reports shows that 34 countries in SSA (72%) have quality control laboratories in place, at different stages of development; 21 of these (63%) are engaged in market surveillance [33]. There are nine WHO Prequalified Laboratories in seven African countries, namely: Adcock Ingram Limited and Research Institute for Industrial Pharmacy incorporating CENQAM (South Africa); National Pharmaceutical Control Laboratory (Algeria); Laboratory of the Mission for Essential Drugs and Supplies and National Quality Control Laboratory (Kenya); Medicines Control Authority of Zimbabwe (MCAZ) QC Laboratory (Zimbabwe); NDA—National Drug Quality Control Laboratory (Uganda); TFDA QC Laboratory (Tanzania); and the National Medicines Quality Control Laboratory (Morocco) [38]. In addition, six QC laboratories in Africa are ISO 17025 Certified [39]. These are; the Ethiopian Food, Medicine and Health Care Administration and Control Authority (FMHACA) Laboratory Services Division (Ethiopia); Centre for Pharmaceutical Advancement and Training (CEPAT) Accra, and Food and Drugs Authority Laboratory (Ghana); Inlab Laboratoria de control de qualidade Inpharma (Cape Verde); and MCAZ (Zimbabwe) and TFDA (Tanzania).

Effective and efficient quality-control laboratories provide a useful infrastructure for PMS activities that are critical to address the challenge of the prevalence of SSFF medical products in Africa.

Clinical trials oversight In view of the high burden of diseases affecting Africa and other developing countries in the world, clinical trials are needed to develop new and effective drugs and vaccines for diseases such as HIV, TB and malaria [6, 21, 40, 41]. The increasing evidence of a shift in the location of clinical trials from industrialised to developing countries, particularly in Africa, requires an independent and strong regulatory and ethical oversight of clinical trials to ensure the safety of research subjects and scientific integrity of clinical data.

Prior to 2006, regulation of clinical trials was limited to ethics review by ethics committees (ECs) in most countries in Africa with the exception of South Africa, where there was an existing level of expertise in clinical trials oversight. Problems were compounded by a lack of legislative and regulatory frameworks for regulation of clinical trials of medicines that would keep pace with new trends in drug research and development [42, 43]. The initiation of the AVAREF by WHO in 2006 with an initial 19 member-countries, paved the way for improved performance in the approval of clinical trials for vaccines through a network of regulatory authorities and ethics committees [44, 45]. The AVAREF has, over the years, facilitated approval of important vaccines such as the conjugate meningitis A vaccine, which has contributed to reduction of meningitis epidemics [46, 47]. With the expansion to 23 member-countries, AVAREF has also served as a collaboration platform bringing regulators, ethics committees and sponsors together to reach consensus on key ethical and regulatory questions, particularly in addressing challenges of authorising clinical trials of Ebola candidate vaccines with limited available data in West Africa [48].

Further initiatives, which additionally promote the safe and ethical conduct of trials in Africa, include the European and Developing Countries Clinical Trials Partnership [42, 49]; the AMRH Initiative [2]; the Initiative to Strengthen Health Research Capacity in Africa [43] and the Pan-African Clinical Trials Registry (PACTR), which was established in 2012 [50]. The latter was designed to increase clinical trial registration, provide an open-access platform for free registration of clinical trials and serve the needs of Africans. PACTR, based in South Africa, works in

collaboration with the Cochrane Infectious Diseases Group, the Cochrane HIV/AIDS Group and WHO.

3 Opportunities for Improving Regulatory Capacity in Africa

The AMRH Initiative, established since 2009 as part of the African Union (AU) Pharmaceutical Manufacturing Plan for Africa (PMPA), aims to improve the fragmented regulatory systems, reducing lead-time associated with meeting different country requirements and contributing to increasing availability of safe, effective, quality essential medicines for priority and neglected diseases [51]. The initiative is focused on changing from a country-focused approach to a collaborative regional approach starting by harmonizing and streamlining technical requirements for product registration and eventually expanding the scope to other product categories (e.g. NCE, vaccines, medical devices and diagnostics) and regulatory functions (e.g. clinical trials, safety surveillance).

The AMRH Initiative has worked through Regional Economic Communities (REC), with an initial pilot in the EAC region starting with harmonised guidelines for registration of medicines and GMP, QMS and Information Management Systems (IMS). As a result, NMRAs in the EAC and SADC regions have conducted joint assessment of dossiers through Collaborative Regulatory Procedures (CRP) to review applications for registration of medicinal products jointly. NMRAs in the two regions have also conducted joint GMP inspections of manufacturing sites to facilitate faster MA of products [52]. A recent pilot study conducted by Janssen Pharmaceuticals Inc., has shown that CRP work in the EAC region has led to a reduction in drug approval timelines by about 40–60% for a number of branded medicines [53]. Initiated by Zambia, Zimbabwe, Botswana and Namibia in 2013, the Zazibona approach in the SADC region has reduced the median timeline from dossier submissions to national MA to 8 months, through CRP.

Coherence of policy and legal frameworks is another AMRH milestone which has resulted in the endorsement by the AU Heads of State and Government, in 2016, of the Model Law on Medical products Regulation, to act as a reference guide to AU Member States as they update or enact national laws [54]. Since its endorsement, 12 out of 55 countries have either reviewed or are in the process of reviewing their national laws, in line with the AU Model Law. These countries are: Ivory Coast, Burkina Faso, Seychelles, Zimbabwe, Lesotho, Namibia, Swaziland, the Gambia, United Republic of Tanzania (Zanzibar), Republic of Rwanda, Republic of Burundi and the Republic of Mozambique. The AU Model Law also facilitates countries' participation in harmonization efforts through RECs.

The launch in 2014 of 11 Regional Centres of Regulatory Excellence (RCOREs) is another key milestone which aims to address the challenge of insufficient regulatory experts in Africa [55]. RCOREs are responsible for increasing the regulatory workforce in Africa by providing sustainable training programmes in regulatory science; promoting operational research; contributing to skills enhancement by hands-on training, twinning and exchange programmes; and practical training through placement of trainees in the pharmaceutical industry. The designated RCOREs are specialised in quality assurance and quality control, PV, clinical trials oversight, medicines registration and evaluation, as well as licensing of manufacturers, inspection and surveillance, among others.

Since 2009, the United States Pharmacopeia (USP) has facilitated the establishment of a Network of Official Medicines Control Laboratories (NOMCOL) in Africa to provide a forum for sharing best practices on medicines quality issues at regional and national levels. The network offers unique inter-laboratory testing activities for participating laboratories to improve performance, as well as harmonize their drug analysis methodologies [56]. For sub-Saharan Africa (NOMCOL-SSA) the network comprises 16 member-countries: Botswana, Burundi, Cote d'Ivoire, Ethiopia, Ghana, Kenya, Liberia, Mali, Mozambique, Nigeria, Senegal, Sierra Leone, Tanzania, Uganda, Zambia and Zimbabwe [57]. Further North, Algeria, Egypt, Morocco, and Tunisia fall under NOMCOL—Middle East/North Africa (NOMCOL-MENA). A total of 23 African countries (43%) have benefited from the USP support to this network.

The opening up of AVAREF forum to all 55 African countries provides a good platform for extending support across the continent. The ongoing work to align AVAREF with AMRH will provide a comprehensive framework for ethics and clinical trial oversight for Africa to accelerate the development of new or improved medical interventions for poverty-related neglected diseases affecting the African population and provide a platform for preparedness during public health emergency. The WHO Prequalification Programme also provides a useful platform for regulatory systems strengthening and harmonization [58].

The AU Executive Council's recognition of the need to strengthen the capacity for regulation of medical products and promote harmonization serves as a foundation of establishment of the centralised African Medicines Agency (AMA). Such a body is expected to work collaboratively with NMRAs to facilitate coordination of regional harmonization efforts, provide technical guidance and ensure sustainability and reduce duplication of efforts ensuring cost-effective use of the scarce resources. In the context of AMRH and PMPA, this will provide an opportunity for sustaining the current momentum in regulatory progress that has been observed in the continent [59].

4 Conclusion

The regulatory landscape in Africa has changed remarkably over the past few years. Apart from the Sahrawi Republic, every country in Africa currently has a NMRA; although, the functionalities are variable across countries and they are at different levels of growth, maturity and expertise. At least 35 African countries (64%) are members of PIDM with South Africa, Morocco, Nigeria, Egypt and Kenya classified as the main ICSR reporting countries. Thirty-four counties in SSA (72%) have quality-control laboratories with different levels of development, and 21 of these (63%) are engaged in market surveillance. However, there is a need to benchmark African NMRAs in a more transparent and objective manner, based on agreed criteria, to identify the different levels of capacities and performance. The outcome of the benchmarking process will be useful to support the ongoing harmonization efforts and facilitate capacity building among the agencies including twinning arrangements and sharing of best practices. The ongoing regulatory systems strengthening and harmonization efforts, such as AVAREF, AMRH and the planned establishment of the AMA, provide opportunities for improvement.

Compliance with Ethical Standards

Conflict of interest Margareth Ndomondo-Sigonda, Jacqueline Miot, Shan Naidoo, Alexander Dodoo and Eliangiringa Kaale have no conflicts of interest.

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REVIEW ARTICLE

The African Medicines Regulatory Harmonization Initiative: Progress to Date

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Abstract

The African Medicines Regulatory Harmonization Initiative (AMRH) has contributed to reduce marketing authorization timelines in East African Community and the Southern African Development Community member states. Challenges still exist in using the outcome of the regional joint dossier review processes for national decision making processes by the national medicines regulatory agencies.

Progress in domestication of the African Union Model Law on Medical Products Regulation by twelve countries provides basis for improving regulatory systems. This is coupled by the designation of eleven regional centers of regulatory excellence which will ensure sustainable training programmes and subsequent increase in Africa's regulatory workforce.

The Biennial Scientific Conferences on Medical Products Regulation in Africa is a strategic platform for knowledge and ideas exchange among key stakeholders in the pharmaceutical sector. The ongoing alignment of the African Vaccines Regulators Forum, the Network of Medicines Control Laboratories in Sub-Saharan Africa, Pan African Harmonization Working Party on the regulation of medical devices and diagnostics, the planned establishment of a forum for blood and blood with AMRH serves as a solid foundation for establishment of the African Medicines Agency (AMA). AMA will be a key driver to remove technical barriers for trading among the region countries by contributing to the continental socio-economic development agenda.

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Key points:

1. The African medicines regulatory harmonization has improved registration timelines in East African Community and Southern African Development Community.
2. The African Union Model Law on Medical Products Regulation and Regional Centres of Regulatory Excellence serve as useful tools for improving regulatory capacity in Africa.
3. Alignment of regulatory systems strengthening and harmonization efforts provide a foundation for establishment of the African Medicines Agency.

1. Introduction

Marketing authorisation (MA) and clinical trials authorization (CTA) for global health products such as vaccines and medicines in many low- and middle-income countries (LMICs) have experienced delays ranging from 4-7 years in comparison to most of high-income countries (HICs) [1]. In Africa, barriers causing these delays include weak or non-coherent regulatory standards and requirements among countries; lengthy medicine registration processes that lead to delays in approval decisions; technical capacity and capability; overall resource constraints; and failure to leverage regulatory review activities already performed by better-resourced regulatory authorities and the World Health Organization (WHO). In addition, delays in CTA have been largely attributed to the lack of role clarity and transparency between national medicines regulatory authorities (NMRAs) and national ethics committees (NECs) [1].

Conception of the African Medicines Regulatory Harmonization (AMRH) Initiative in 2009 was driven by the need to remove these barriers that hinder patient access to healthcare products in Africa [2]. The AMRH initiative's aim is to support African countries to overcome these constraints by building effective medicines registration through regional harmonization and capacity building [3]. A consortium of partners comprised by NEPAD Agency, African Union Commission (AUC), Pan African Parliament (PAP), WHO, Bill and Melinda Gates Foundation (BMGF), the UK Department for International Development (DFID) and Clinton Health Access Initiative (CHAI) was established to facilitate the needed political, technical and financial support required by NMRAs working through their respective regional economic communities (RECs) [3]. A global medicines regulatory harmonization multi-donor trust fund (GMRH-MDTF) was created in 2011 under the fiduciary oversight of the Word Bank to promote the harmonization of medicines regulations, strengthening governance and regulatory systems [4].

Leveraging on NEPAD Agency's continental reach and its mandate as the technical arm of the African Union (AU) with WHO providing technical lead role, AMRH has launched regional Medicines Regulatory Harmonization (MRH) projects that have proven to be instrumental in guiding NMRAs to determine priority areas of action for medicines regulatory strengthening and harmonization in Africa [3]. With initial funding from the Bill and Melinda Gates Foundation (BMGF), the GMRH-MDTF has enabled pooling of donor funds, assure fiscal accountability, drive projects through the Bank's in-

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country management capabilities and ensure that RECs receive the necessary resources in a flexible and coordinated manner. Other donors who have committed or contributed to the fund include DFID, US Government/PEPFAR and GAVI, International Federation of Pharmaceutical Manufacturers Associations (IFPMA). Contributions outside the Trust Fund were received from the Swiss Agency for Development and Cooperation (SDC), World Bank SWEDD (Sahel Women Empowerment and Demographic Dividend) project and BMGF for clinical trials authorization through the AVAREF Additionally, the BMGF made grants to NEPAD Agency for coordination, communication and advocacy, and to WHO to support the African Vaccine Regulatory Forum (AVAREF) for harmonization and regionalization of CTAs. The initiative received policy and political backing under the AU Pharmaceutical Manufacturing Plan for Africa (PMPA), which specifically recognises the need for African countries to strengthen their medicines regulatory systems by pooling their resources in order to achieve public health policy priorities [3, 5].

The aim of AMRH Initiative is to improve the fragmented regulatory system for product registration in Africa by changing from a country-focused approach to a collaborative regional and simplified one [3,6]. The AMRH pathway is to use regional regulatory platforms to harmonise technical requirements and guidelines for registration of medicines, conducting joint regional dossier assessments and good manufacturing practice (GMP) inspections, work sharing and pooling of resources with subsequent streamlined decision-making process at national level. The end result is a reduced registration cycle time starting with generics and extending to other product categories such as new chemical entities (NCEs), vaccines, diagnostics and further extending to other regulatory functions over time such as clinical trials, safety surveillance, just to mention a few. The plan was to pilot in one regional economic community for learning before extending to other African regional blocs.

This review paper aims to provide an overview of the AMRH initiate including documented successes so far on collaboration in MA of medical products; pharmacovigilance and ongoing alignment of similar initiatives. It will serve as a pre-cursor for an in-depth analysis of the East African Community (EAC) medicines regulatory harmonization (MRH) project to identify gaps, challenges and opportunities for improvement. Lessons learnt from other RECs will also be explored with a view to provide recommendations for a sustainable mechanism for transitioning the AMRH into the African Medicines Agency (AMA).

The paper is structured in a way that provides baseline status of medicines regulation before AMRH inception; progress on harmonization of registration requirements and joint assessment in RECs; the status of implementation of AU Model Law on medical products regulation; efforts to accelerate the fight against sub-standard and falsified medical products and approaches to institute sustainable regulatory capacity development programmes. The paper further provides strategies for implementing phase two of the AMRH Initiative focusing on CTA, pharmacovigilance and post marketing surveillance; as well plans for alignment of various regulatory systems strengthening and harmonization initiatives as a foundation for establishment of the AMA.

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2. Baseline assessment and development of regional medicines regulatory harmonization projects

Prior to the launch of regional MRH Projects, AMRH partners conducted a situation analysis of the status of medicines regulation in the EAC, the Southern African Development Community (SADC) and the Economic Community of West African States (ECOWAS). The assessment in the EAC region indicated variation in countries laws and regulations, absence of a mutually recognized legal framework and marked differences in capacity among the NMRAs within the region [7]. Reports in SADC and ECOWAS regions revealed similar results with varying comprehensiveness of legal frameworks between countries which in turn affects the capacity to effectively regulate the market [8, 9, 10]. The inconsistency between regulatory frameworks and procedures within RECs and within the African region more broadly imposes further burdens on both innovator and generic pharmaceutical manufacturers, who face the added expense of adapting MA requirements to the particularities of different countries [1]. The implication of these findings is that there's not only an efficiency loss for manufacturers and registrants of medicines, but there is also considerable and inefficient efforts duplication by over-burdened NMRAs, resulting in delays that ultimately impact on patient health [1].

As a result of these studies, regional MRH projects were developed with the initial funding and launching of the EAC MRH Project in 2012 followed by SADC and ECOWAS MRH Projects launched in 2015. The EAC MRH Project specifically aimed to; implement an agreed common technical document for registration of medicines in EAC Partner States; implement a common information management system (IMS) for medicines registration in each of the EAC; build a quality management system (QMS) in each EAC Partner States' NMRAs; construct regional and national capacity to implement medicines registration harmonization in the EAC; create a platform for information sharing on the harmonized medicines registration system to key stakeholders at national and regional level; and develop as well implement a framework for mutual recognition based on Chapter 21, Article 118 of the East African Community Treaty [11, 12]. The EAC MRH project marked the beginning of the implementation phase of the AMRH initiative across Africa, aiming to achieve a harmonized medicines registration process in its member countries – Uganda, Kenya, the United Republic of Tanzania, Rwanda and Burundi – based on common documents, processes and shared information systems [13].

In the SADC region, an MRH Project proposal was developed by NMRAs with support from the AMRH Partners in 2011. Due to limited funding under the GMRH-MDTF, a DFID funded project, the Southern African Regional Programme Access to Medicines and Diagnostics (SARPAM) initiated and supported a ZAZIBONA scheme among four (4) NMRAs in the SADC region since October 2013. The founding member countries of ZAZIBONA scheme namely; Zambia, Zimbabwe, Botswana and Namibia agreed to work together under a collaborative procedure for medicines registrations technically supported by WHO [14]. This was part of breakthrough activities in support of implementation of a broader MRH Project developed in 2011. It was during the same year when the MRH Project for ECOWAS region was developed and validated by the NMRAs in the region under the coordination of the West African Health Organization (WAHO) in

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collaboration with the West African Economic and Monetary Union (WAEMU). The SADC and ECOWAS MRH Projects were officially launched in 2015 [15].

3. Progress on harmonization of registration requirements and joint assessments in RECs

3.1. EAC: As of April 2017, the EAC Joint Assessment Procedure received a total of 32 applications, of which 27 were evaluated, resulting in 4 product registrations and 23 applications queried with an estimated 30 - 40% faster completion of evaluation procedure than the national levels, resulting in significant cost and time savings [11]. In 2015/2016, the median timeline from dossier submissions to national marketing authorization in the EAC region was reduced to seven (7) months since implementation of joint dossier assessments compared to the previous 1 – 2 years [16]. A recent study conducted by Janssen Pharmaceutica Inc. showed a reduction of approval times by 40 – 60% for a number of branded medicines through joint dossier assessments in the EAC [17].

3.2. SADC: Building on the success of the EAC MRH project joint dossier assessments, the SADC region initiated a platform in 2013 called ZAZIBONA, initially composed of Zambia, Zimbabwe, Botswana and Namibia to coordinate joint assessments in the region. The ZAZIBONA process was established with a view to facilitate availability of good-quality medicines through work-sharing in assessment of medicines and inspection of medicine manufacturing and testing facilities. The aim is to significantly reduce time taken to grant MA in the individual countries; and ensure efficient utilisation of resources among NMRAs in the region through work sharing [18]. The ZAZIBONA initiative has evaluated 179 product applications over 15 meetings from October 2013 with a final decision reached for more than 90 products and a mean time to recommendation estimated at nine months [19,20]. While the ZAZIBONA scheme was officially adopted as a SADC MRH Programme in 2014, a total of ten (10) countries (including the four founding members) have now joined the scheme with different membership status including; South Africa, (active), Swaziland (active), Democratic Republic of Congo (active), Angola (non-active), Seychelles (non-active) and Malawi (non-active) [16].

3.3. Implementation of MRH Projects in other RECs: Implementation of MRH regional projects has stretched from SADC and EAC regions to include West Africa where WAHO and WAEMU are working collaboratively to implement a common technical document. A joint dossier assessment will be initiated in 2017 with technical support from WHO. The Economic and Monetary Community of Central Africa (CEMAC) region has established since 2016, a Steering Committee to provide oversight on MRH Project and SF products under the leadership of the Organization of Coordination for the Fight Against Endemic Diseases in Central Africa (OCEAC). Similarly, Member States NMRAs of

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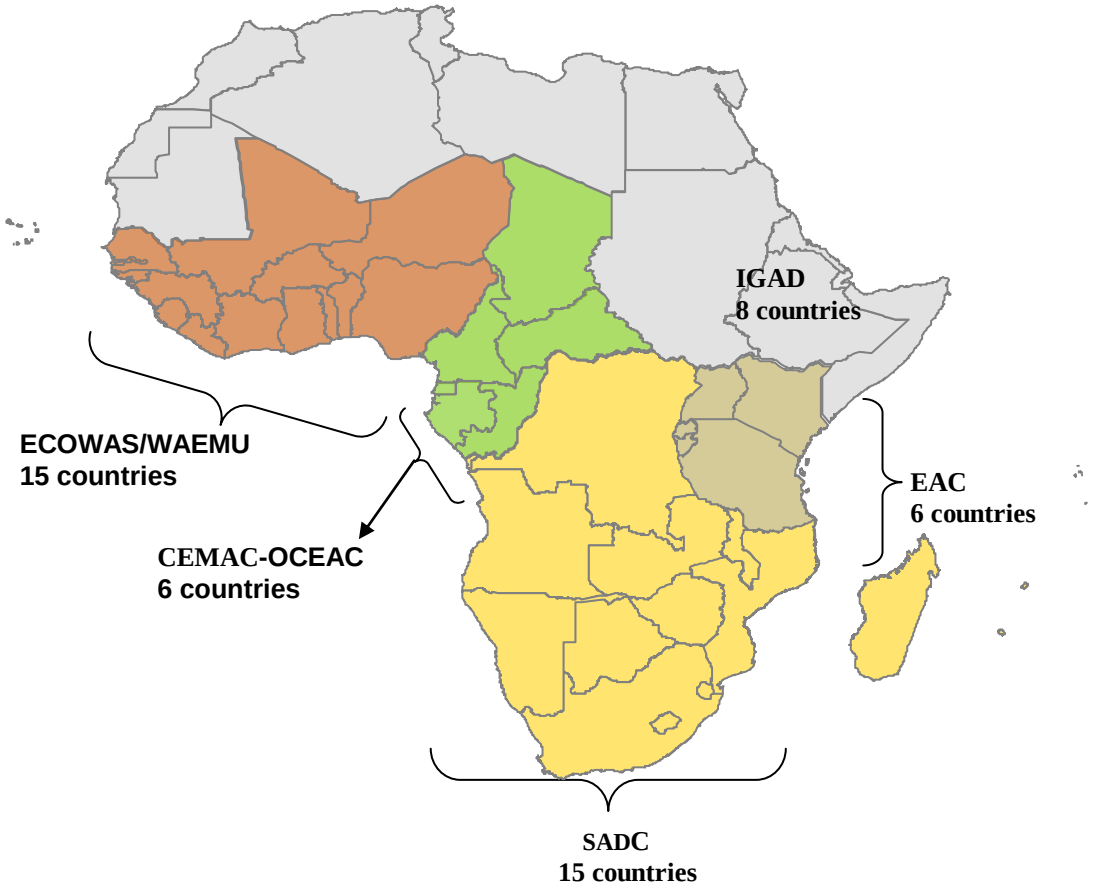
the Intergovernmental Authority on Development (IGAD) have agreed and signed the Call for Action to initiate the implementation of a regional MRH Project since 2016. The overall coverage of the AMRH Initiative across the continent is more than 85% as indicated below in **Figure 1**.

Figure 1: AMRH Coverage across Sub-Saharan Africa

> 85% of Sub-Saharan Africa covered with medicines registration harmonization (MRH) Projects at different levels of implementation



Source: AMRH Publications

Key:
CEMAC - The Economic and Monetary Community of Central Africa
EAC – East African Community
ECOWAS – Economic Community of West African States
IGAD - Intergovernmental Authority on Development
OCEAC - Organization of Coordination for the Fight Against Endemic Diseases in Central Africa
WAEMU – West African Economic and Monetary Union

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

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Here it is important to note that, while positive progress has been registered on the implementation of regional MRH Projects, there is need for a critical review of the existing regional joint review processes undertaken in EAC and SADC through ZAZIBONA approach to determine the best option which will ensure efficiency and effective decision making process at country levels. On this regard it is important to consider variations in regulatory capacities among countries, regions size and different historical heritage among countries.

4. The Status of implementation of African Union (AU) Model Law on Medical Products Regulation

In order to address the barrier of non-existent, weak or non-coherent medicines laws in African countries, the AMRH Initiative developed the AU Model Law on medical products regulation to ensure effective regulation and promote harmonization [21, 22]. The Model Law endorsed by the AU Assembly in January 2016, is at different levels of domestication and implementation by twelve (12) African countries. These countries are: Ivory Coast, Burkina Faso, Seychelles, Zimbabwe, Lesotho, Namibia, Swaziland, the Gambia, United Republic of Tanzania (Zanzibar), Republic of Rwanda, Republic of Burundi and the Republic of Mozambique [23].

The AU Model Law is available in English, French, Portuguese and Arabic and the aim is to have at least 25 AU Member States using a version of the Model Law on medical products regulation by 2020. In order to facilitate implementation of the AU Model Law, AMRH has established a continental Technical Working Group on Policy and Regulatory Reforms (TWG-PRR) composed of regulators and legal experts from AU Member States, RECs and RHOs to guide the domestication process. Currently, regional roadmaps for implementation of the AU Model Law have been developed and AU Member States are able to update their regulatory frameworks and enact a version of the AU Model Law that befit their country context to strengthen their national regulatory capacity.

According to WHO, "the highest attainable standard of health is a fundamental right of every human being and this right includes access to timely, acceptable, and affordable healthcare of appropriate quality" [24]. The Model Law will contribute to facilitate review or enactment of national laws in Africa in line with international standards contributing to and facilitating availability of medical products.

4.1. Accelerating efforts combat Sub-Standard and Falsified medical products

It is estimated that the pharmaceutical market size in Africa will be worth between USD 40 Billion to USD 65 Billion by 2020 [25]. However, more than 70% of the medicines consumed on the continent are imported making regulation by most of African countries difficult, fuelling illicit transactions of drugs and contributing to health problems [26].. A recent report on counterfeit medicines in Central Africa indicates that illicit trade in drugs accounts for 25% of the pharmaceutical market size in countries where it is poorly developed and up to a high of 55% in countries where it is well developed [27]. Since the problem of sub-standard and falsified (SF) medical products is not unique in Central Africa alone, implementation of the AU Model Law on medical products by AU Member States can assist to strengthen national and regional regulatory systems while at the same time complementing the war against SF medical products through enforcement of a specific provision for prohibition of

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Sub-Standard and Falsified medical products [28, 29].

In addition, NEPAD Agency together with United States Pharmacopeia (USP) and the West African Health Organization (WAHO) have agreed to work together towards transforming the Network of Medicines Control Laboratories in Sub-Saharan Africa (NOMCoL–SSA) into the African Medicines Quality Forum (AMQF) to address the challenge of prevalence of SF medical products on the continent [30]. AMQF will complement the work of the AU Model Law in addressing issues of medicines quality control and post marketing surveillance ensuring that an appropriate legal framework is instituted to facilitate establishment of quality control laboratories as part of the NMRAs. The NOMCOL-SAA is now being co-led by the USP and NEPAD Agency, and expanding in the scope and reach, to cover all African countries as part of the newly developed AMQF. The AMQF will continue to build laboratory and regulatory staff technical capabilities, while also playing an advocacy role to reduce the prevalence of SF medical products in circulation on the African markets [31].

4.2. Instituting sustainable regulatory capacity development programmes

Beyond MRH regional projects, the AMRH also initiated in 2014 a programme to establish Regional Centres of Regulatory Excellency (RCOREs) as part of its mandate to develop and strengthen regulatory capacity in Africa. The AMRH recognizes the importance of regulatory capabilities development in delivering quality healthcare services and addressing regulatory capacity gaps and challenges experienced by NMRAs and the pharmaceutical sector in Africa. As a result, AMRH, through the NEPAD Agency, has designated a total of 11 RCOREs in eight (8) different regulatory functional areas across the continent. [32]. The USP Centre for Pharmaceutical Advancement and Training (CePAT) in Ghana serves as a Reference Centre of Regulatory Excellence (RefRCORE) for NEPAD, providing capacity building support and expertise to the 11 RCOREs.

RCOREs are institutions or partnership of institutions with specific regulatory science expertise, as well as training capabilities and their role is to produce regulatory workforce in Africa through performing four (4) key functions. These include; providing academic and technical training in regulatory science applicable to different regulatory functions and managerial aspects; contributing to skills enhancement through hands-on training, twinning and exchange programmes among NMRAs; encouraging practical training through placement pharmaceutical industry; and spearheading operational research to pilot-test innovations and interventions to inform best practices and promote scaling up activities [13]. RCOREs have been designated in the following key areas; pharmacovigilance, clinical trials oversight, quality assurance and medicines quality control , medicines registration and evaluation, licensing of manufactures, importers, exporters, distributors, inspectors and surveillance, as well training in core regulatory functions. The eleven (11) designated RCOREs in different areas of regulatory expertise are indicated in **Figure 2.**

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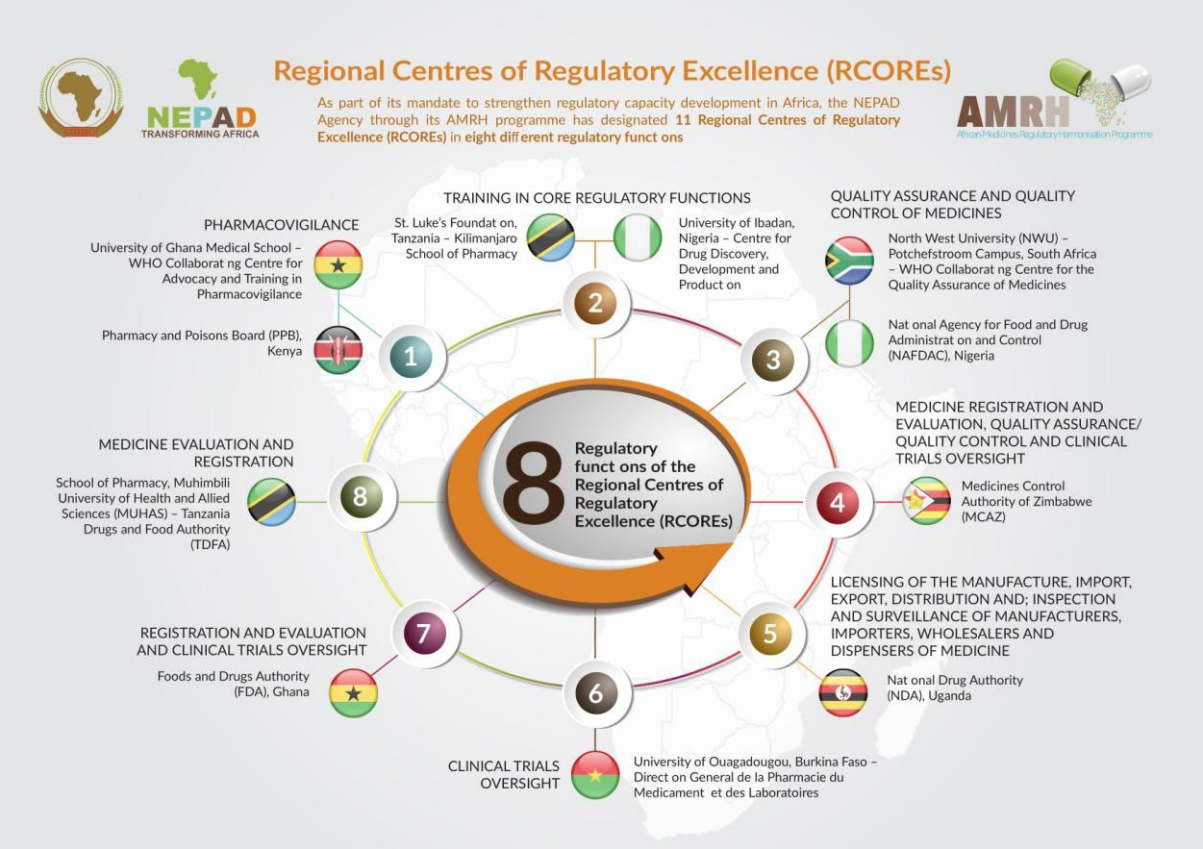
Figure 2: AMRH Regional Centres of Regulatory Excellence



Source: NEPAD AMRH Publications, 2017

4.3. Biennial Scientific Conferences on Medical Products Regulation in Africa:

In addition to RCOREs, AMRH also initiated the Biennial Scientific Conferences on Medical Products Regulation in Africa (SCoMRA) as a continental platform for sharing lessons learnt and best practices, facilitating networking and collaboration, reflect on the work accomplished so far and rejuvenate actions towards sustaining the momentum for regulatory strengthening and harmonization in Africa. The Scientific Conference sets the medicines regulatory strengthening and harmonization agenda for the future through strategic exchange of knowledge and ideas. The inaugural Biennial Scientific Conference was held in Johannesburg, South Africa in 2013 with the theme *Building Partnerships for Sustainable Capacity Development in Medicines Regulation in Africa*. This was followed by the 2nd Biennial Conference which took place in 2015 in Addis Ababa, Ethiopia under the theme *Regulatory Systems Strengthening for Advancing Research, Innovation and Local Pharmaceutical Production in Africa*. In 2017, the theme of the 3rd Biennial Scientific Conference is *Sustaining the Momentum for Regulatory Harmonization in Africa* and will take place in Accra, Ghana from 27 – 28 November 2017. It will be the first time that the Biennial Scientific Conference is held at the same time as the AVAREF Assembly which will take place on 29 November 2017 in the spirit of collaboration and harmonization. These will

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also be followed by the African Medicines Regulators Conference (AMRC) from 30 November to 01 December 2017 [33].

5. Alignment of regulatory systems strengthening and harmonization efforts as a foundation for AMA

The original thinking under the AMRH Initiative has been to gradually expand the scope of work from registration of generic medicines to other regulatory functions and products including oversight on vaccines clinical trials, pharmacovigilance, New Chemical Entities (NCEs), medical devices and diagnostics, just to mention a few; and a step-wise geographical expansion to cover all African countries [34]. Expansion of the scope of this work demands improved coordination and harmonization of the different partners and stakeholders to avoid duplication, fragmented priorities and ensure resource optimization.

In order to ensure alignment and define the next scope, AMRH Partners convened a strategic workshop in February 2017 bringing together AMRH global partners, regional and national stakeholders to plan on implementation of phase two of the Initiative [35]. *A five year strategic direction and establishment of a lean governance structure for the successful implementation of phase two of the programme were agreed*. Furthermore, there was consensus reached on realignment of other similar programmes with AMRH activities to provide end to end programme impact in Africa from CTA, MA to safety surveillance of medical products. NEPAD Agency was identified as the hub that shall hold the coordinating role to bring together new and existing actors working in these areas to avoid duplication of activities and ensure maximum utilization of the already scarce resources in Africa [32]. Subsequently, a Steering Committee on Medical Products Regulatory Systems Strengthening and Harmonization has been established to provide oversight [32].

This implies scaling up the work of AMRH and creating linkages with other similar initiatives on regulation of medical devices and diagnostics, and blood products such as; AVAREF, NOMCoL-SAA and Pan African Harmonization Working Party (PAHWP). This alignment will be coordinated by NEPAD Agency through the AMRH Partnership Platform (AMRH-PP) as Africa chapter of the Global Coalition of Interested Partners (CIP), operating under the oversight of the AMRH Steering Committee [32]. While the existing continental Technical Working Groups (TWGs) under the AMRH Initiative namely, TWG on Regulatory Capacity Development, TWG on Policy and Regulatory Reforms and EWG on Good Manufacturing Practice (GMP) standards will be maintained, new TWG on registration and PV will be established to develop continental frameworks which can be adopted by RECs and NMRAs. Existing networks such as AVAREF and NOMCOL-SAA will be transformed into continental TWGs.

On the PV front, a consensus reached by PV stakeholders in 2015 shall serve as basis for establishment of a continental framework for sustainable capacity development on PV in Africa with a view to assist countries to have a national PV system which meets internationally acceptable standards as recommended by WHO [36]. PV requirements and guidelines will be harmonised to ensure availability of complementary and simplified tools to be used by NMRAs, MA holders and all other stakeholders in PV in Africa. A database of PV experts in Africa, regional expert working groups and an Africa PV Advisory

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Group (APAG) will be established to ensure coordination of the many fragmented PV initiatives on the continent and the development of a coherent framework for PV in Africa. The RCOREs on PV will be used as vehicle for sustainable regulatory capacity development to ensure increased workforce and institutional capacity to undertake training programmes to address Africa's needs and priorities and as a long term strategy to support the ongoing regional MRH Projects. Advocacy for increased investment by international partners and governments on PV including financial and technical resources is key.

AVAREF, as a regional regulatory network founded in 2006 by WHO, was initiated at a time when the focus on clinical trials of vaccines began to shift from developed countries to developing countries, including those in sub-Saharan Africa [37]. Starting with nineteen (19) NMRAs and ethics committees of the countries in the WHO African region, the forum had expanded to 23 member countries by 2016 when a new governance structure was agreed. The New AVAREF Goal is to strengthen clinical trials regulatory authorization and oversight in Africa by increasing system's efficiency and building an optimal clinical trial infrastructure through harmonized requirements for CTA and ethics committee approval, to develop and implement guidelines for joint review of clinical trial applications at regional or multi-country level for vaccines and drugs candidates [38]. Key among AVAREF's achievements has been the establishment of innovative regulatory pathways for clinical trials; the development and use of common guidelines for submission of clinical trial applications, and the use of joint reviews of multi-country clinical trial applications and joint good clinical practice (GCP) inspections. As a result, AVAREF has registered improved timelines for product development joint reviews and GCP inspections have played a key role in ensuring timely regulatory authorization and approvals of MenAfriVac®, the meningococcal A conjugate vaccine whose rollout in the meningitis belt of Africa has eliminated epidemic meningitis due to Group A Neisseria meningitides as a public health problem [37]. A joint review approach was also used to coordinate and expedite the review of the multi-country Phase III clinical trial for the lead malaria candidate vaccine, RTS,S/AS01, which is about to conclude in seven African countries. The platform that has been instrumental in providing regulatory support to accelerate product development during public health emergencies, as exemplified with products in development against Ebola [37]. In view of these achievements, AVAREF future is destined to support the work of African regulators on vaccines for diseases such as HIV, tuberculosis and malaria, which are affecting millions of people on the continent.

Concrete achievements registered under AMRH and AVAREF serve as a foundation for establishment of AMA in line with the call by the AUC-WHO Joint meeting of the Ministers of Health held in 2014 in Luanda, Angola and the AU Executive Council Decision EX.CL/DEC.857 (XXVI) of 2015 [39, 40, 41]. The AU leadership has called upon Member States to prioritize investment for regulatory capacity development; to pursue the efforts towards convergence and harmonization of medical products regulation in RECs and to allocate resources for the operationalization of the AMA [42]. The AMRH and AVAREF success stories provide an enabling reg-ulatory environment for research and development, innovation and local production of pharmaceuticals, optimizing competitiveness and expanding market [32].

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It is important to note that Africa needs strong institutions that can address the challenges of access to quality, safe and efficacious medical products and technologies, so establishment of the AMA is a very important step in the right direction [42]. AMA does not seek to replace NMRAs national sovereignty, instead it will complement NMRAs, RECs and RHOs' efforts in the process of establishing an enabling environment for the development of the pharmaceutical industry through better coordination of different partners and stakeholders undertaking medicines regulatory strengthening and harmonization efforts on the continent [43] [44]. It is therefore necessary for Africa to lay a sound ground for pharmaceutical market growth while at the same time taking advantage of the increasing political stability; rapid economic development; increasing investment in public health; maturing regulatory environment; and rising consumerism [45].

Sustaining the AMRH and AVAREF momentum and a smooth transition into AMA will contribute to reducing technical barriers to trade especially at this time when the RECs are rapidly moving towards stronger economic integration [3]. The EAC Common Market and the Customs Union which have been operational since 2010, are just some examples [46].

6. Conclusion

Phase one of the AMRH Initiative has recorded significant success in harmonising registration requirements and facilitating joint reviews of dossiers in EAC and SADC with resultant reduction in approval timelines. Review of gaps in the regional joint review process is critical to inform scale up to other RECs. Phase two of the AMRH Initiative entails expansion of regulatory scope and products including establishing continental frameworks for registration of medical products, CTA, PV and PMS. The AU Model Law on Medical Products Regulation and RCOREs will facilitate improvement in regulatory capacity.

Looking forward, AMRH will continue to work towards improving medicines regulatory and harmonization landscape in Africa in line with its vision of ensuring that African people have access to the needed essential medical products and technologies. Alignment of regulatory systems strengthening and harmonization efforts and advocating for establishment of AMA is key for optimizing pharmaceutical markets and sustainability in the supply of medical products and technologies for diseases disproportionately affecting Africa.

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RESEARCH ARTICLE

National medicines regulatory authorities financial sustainability in the East African Community

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Abstract

Introduction

Adequate and sustainable funding of national medicine regulatory agencies (NMRAs) is key for assurance of quality, safety and efficacy of medical products circulating in a market. The study aimed to determine factors affecting NMRAs funding in five East African Community (EAC) countries namely: Burundi, Kenya, Rwanda, Tanzania (Mainland and Zanzibar) and Uganda.

Methodology

An exploratory, mixed method design using both qualitative and quantitative data, was employed. Data from six NMRAs was collected through a combination of semi-structured interviews, questionnaires, and checklists for the period 2011/12-2014/15 while 2010/11 data served as baseline. Interviews were conducted with heads of NMRAs and monitoring and evaluation experts of the respective agencies. NMRA's financing was assessed using six indicators namely, funding policy, financial autonomy, the total annual budget, actual funding per annum, funds received from various sources, and the NMRA expenditure.

Results

The average total annual budget for all the EAC countries during the study period 2011–2015 ranged from USD 824,328.67 to USD 10,724,536.50. The low budget in Zanzibar may be attributed to population and pharmaceutical market size. Uganda's attainment of 98.75% (USD 10,656,704) revenue from industry fees is a result of deliberate government policy change from 100% reliance on donor funding over a period of 10 years (1995–2015). On average, the proportion of revenue against budget per annum is 54.8% (USD 458,970.11),

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98.7% (USD 10,302,295.25) and 100% (USD 7,375,802.08) for Zanzibar Food & Drugs Agency (ZFDA), Uganda National Drug Authority (NDA) and Tanzania Medicines and Medical Devices Authority (TMDA) respectively. Governments, industry fees and donors are the major sources of funding across all NMRAs in the EAC region, with TMDA and Uganda NDA relying more on industry fees by 73.20% (USD 4,664,777.59) and 98.25% (USD 8,077,238.20) respectively. While Burundi relies solely on government funding, ZFDA, on the other hand, received on average 50.40% (USD 252,557.22) from government and 40.60% (USD 165,303.34) from industry fees and the remaining 9% from donors and other sources. An overall contribution of funds received from donors by each NMRA was the least among other sources of financing. Observation of expenditure patterns indicated operational costs to be the major expense in the majority of the NMRAs, followed by salaries and infrastructure development. The Kenya NMRA has the highest degree of average expenditure across all three categories, with the least average expenditures being marked by Burundi NMRA. The operational costs on average increased considerably in all the NMRAs during the study period.

Conclusion

Evidence from the EAC suggests that government and industry fees are the main sources of funding while donor contributions vary from country to country. Government policy, legal framework, and fees structure are the key enablers of NMRAs funding sustainability.

Introduction

National Medicines Regulatory Agencies (NMRAs) are responsible for carrying out a number of regulatory functions including: registration and marketing authorization, vigilance, market surveillance and control, licensing establishments, laboratory testing, clinical trials oversight and NMRA lot release, just to mention a few [1]. All these activities require adequate financial resources to assure the quality, safety and efficacy of medical products on the market and promotion of patient safety as a critical part of the health care delivery system [2]. Studies show that this important task of regulating medical products is often under-funded and under-recognized in many countries in Africa [2].

Sustainable funding is one of the key factors to ensure effective regulation of medical products, others include a comprehensive legal framework, appropriate and adequate governance mechanisms, and sound technical expertise [3]. The legal basis gives the NMRA power to perform a function. However, there are a number of prerequisites to its performance. These include, the level of autonomy in executing its mandate, the appropriate structure that allows for proper coordination of various regulatory activities, availability of financial resources and adequate number and type of appropriately skilled human resources with requisite competency to carry out their duties [4].

Sustainability of financial resources for NMRAs means having a specific budget assigned to medicines regulation and assurance that the allocated funds are safeguarded against the competing needs of other government agencies [4]. NMRAs funding sources can be derived from public funding, fees for services provided and donations to supplement the often limited funding available from government [5,6]. The stability of an NMRA depends on its financing mechanism [6].

Globally, medicines regulators struggle with the need for financial and technical resources to fully meet their mandate. Generally, NMRAs from well-resourced countries such as the United States of America have reliable funding. For instance, the US Food and Drug Administration (US-FDA) budget for 2019 financial year is estimated at USD 5.7 billion, 55% of which (USD 3.1 billion) is provided by the federal government and the remaining 45% (USD 2.6 billion) is paid for by industry user fees [7]. In the United Kingdom, the Medicines and Healthcare products Regulatory Agency (MHRA) employs mixed funding arrangements where the Department of Health and Social Care) (DHSC) funds regulation of medical devices, whilst the costs of medicines regulation is met through fees from the pharmaceutical industry [8]. Studies conducted in Sub-Saharan Africa, on the other hand, have shown that in nine out of the twenty six States studied (34.6%) the NMRAs depend on government funding with all fees paid directly to treasury and not redistributed. In addition funds allocated by the States to their respective NMRAs are not released on time [5].

Due to limited publications on sustainable financing models for NMRAs, especially in low-middle income countries, this study is intended to contribute to the existing knowledge on the various funding sources for NMRAs, factors affecting sustainability and to propose sustainable funding options using the East Africa Community (EAC) as a case study.

Methodology

An exploratory, mixed method design using both qualitative and quantitative data, was employed in this study. Data was collected from all the six NMRAs in the EAC partner States namely, the Republic of Burundi, Republic of Kenya, Republic of Rwanda, the United Republic of Tanzania (with two NMRAs), and the Republic of Uganda. Data from six NMRAs was collected through a combination of semi-structured interviews, questionnaires and checklists as indicated in S1 File, for the period 2011/12-2014/15 while 2010/11 data served as baseline.

Questionnaire and checklist were developed based on the information obtained from the preliminary situational analysis study. Moreover, additional questions were adopted from the WHO Global benchmarking tool for evaluation of national regulatory systems [1]. Validation of the questionnaire and checklists was done using a pilot study.

The first phase of data collection involved self-administration of the questionnaire and checklists (S1 File) by the selected informants. These included the NMRA's head, one monitoring and evaluation personnel from each NMRA and a project officer from the EAC MRH project, making a total of 13 respondents. All informants were purposefully selected based on their roles and participation in medicines policy and regulation of medical products in the respective NMRA.

Semi-structured interviews, also involving the above-mentioned respondents, were conducted following the successful completion of the questionnaire and checklists data collection phase. In addition, one NMRA staff responsible for medicines registration, GMP inspections, legal affairs, human resource and finance were also interviewed in each NMRA. An invitation letter and interview topic guide were sent to the interviewees in advance. Interviews were conducted on face to face basis, each session lasting for 1 to 2 hours. Responses were recorded by means of selective written notes, which were thereafter subjected to qualitative analysis. Follow up visits were conducted aiming at collecting the missing data and validating the previously collected data.

Due to lack of data from some agencies, only the available data set was used in statistical analysis and interpretation. The prevailing average annual USD currency exchange rate for each country was used for analysis. The average annual exchange rates of Tanzanian, Kenyan, Ugandan, Rwandese and Burundian currencies against the USD ranged as TZS (1585.3–

2188.2), KES (84.2–101.5), UGX (2349.4–3369.4), RWF (579.9–783.1) and BIF (1159.7–1657.6) respectively over the studied period [9].

NMRAs financing was assessed using six (6) indicators namely: NMRA financing policy, level of NMRA autonomy, the total annual budget for carrying out regulatory functions, actual funding per annum, funds received from various sources, and the NMRA expenditure as shown under indicators guidance notes S2 File.

Quantitative data were analysed for means and standard deviation using Microsoft Excel©, whereas document analysis was used to extract organize and interpret data from policies and laws. This study was part of a larger overall evaluation of the NMRAs implementing medicines regulatory harmonization program in the EAC.

Ethical clearance

Ethics approval was granted by the WITS Human Research Ethics Committee on 31st July 2015 through clearance certificate No. M150751. In addition, national ethical clearance was granted by respective national research ethics committees and ministries of health. Informed consent forms were signed by individual respondents from NMRAs in the EAC partner states.

Results

Funding policies and laws of NMRAs

All six NMRAs provided data on their national medicines policies (NMPs) and medicines laws. While all the NMPs emphasise the need for effective regulation of medical products, policy commitment on funding NMRAs varies across countries. For semi- or fully autonomous NMRAs such as the Tanzania Medicines and Medical Devices Authority (TMDA), the National Drug Authority in Uganda (NDA), the Pharmacy and Poisons Board in Kenya (PPB), the Rwanda Food and Drugs Authority (Rwanda FDA) and the Zanzibar Food and Drug Agency (ZFDA), the laws provide for collection of fees from industry and its utilization to perform regulatory services [10–14]. However, in Burundi, the NMRAs was observed to be fully reliant on government funding during the studied period [15].

Level of NMRA financial autonomy

There has been a progressive transformation of the level of financial autonomy of NMRAs in the EAC region over the study period (Table 1). While Burundi NMRA is not autonomous, the Bill to transform the existing unit to an autonomous agency is at an advanced stage of consideration by her parliament [16]. In Rwanda on the other hand, the Food and drugs act of 2013 [11] has been enacted to establish the Rwanda Food and Drugs Authority (Rwanda FDA) as a semi-autonomous Agency. In Zanzibar, the former Zanzibar Food and Drugs Board (ZFDB) has been transformed into Zanzibar Food and Drugs Agency (ZFDA) by the Zanzibar Food, Drugs and Cosmetics Act number 2 of 2006 [13] with financial autonomy under the oversight of an Advisory Board. The existing laws in Kenya, Uganda and Tanzania-Mainland, provide for financial autonomy and empower the respective NMRAs to collect and utilise fees for services rendered [10,12,14].

NMRAs annual budgets

The average total annual budget for all the countries for the period 2011–2015 ranged from USD 824,328.67 to USD 10,724,536.5 as shown in Fig 1, with Zanzibar and Uganda NMRAs having the lowest and highest average total annual budgets respectively. The NMRAs in Tanzania and Kenya exhibited almost similar average annual budgets, while the data for this

Table 1. Level of NMRA autonomy in the EAC partner states between the years 2011 and 2015.

Indicator	National Medicines Regulatory Agency					
	Burundi	Kenya	Rwanda	Tanzania	Uganda	Zanzibar
NMRA's level of autonomy	Department within the Ministry of Health	Semi-Autonomous	Semi-Autonomous	Semi-Autonomous	Autonomous	Semi-Autonomous
Medicine Law	Republic of Burundi. Decret No. 100/150 du 30 September 1980 portant Organization de l'exercise de la Pharmacie au Burundi. 1980.	Republic of Kenya. The Pharmacy and Poisons Act, Chapter 244. 1957, as amended in 2009.	Republic of Rwanda. Law No. 47/2012 of 14/01/2013 relating to the Regulation and Inspection of Food and Pharmaceutical Products. 2013	United Republic of Tanzania (Mainland). Tanzania Food, Drugs and Cosmetics Act, Cap 219. 2003, as amended in 2004, 2014 & 2019	Republic of Uganda. The National Drug Policy and Authority Act. 1993.	United Republic of Tanzania (Zanzibar). The Zanzibar Food, Drugs and Cosmetics Act. No. 2 of 2006 as amended in 2016

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indicator was not available for Burundi's and Rwanda's NMRAs. When compared to their own baselines, the total annual budget of each NMRA approximately doubled over a duration of five years.

NMRAs annual funding

Comparison of the total annual budget against actual funding per annum shows an average of 54.8% (USD 458,970.11), 98.7% (USD 10,302,295.25) and 100% (USD 7,375,802.08) for Zanzibar Food & Drugs Agency (ZFDA), Uganda National Drug Authority (NDA) and Tanzania Medicines and Medical Devices Authority (TMDA) respectively, for years 2011–2015. However, data from Kenya and Rwanda under this aspect was not available (Fig 2). The 54% funding for ZFDA may entail either a problem with setting an unrealistic budget or simply that funding was inadequate to support NMRA activities.

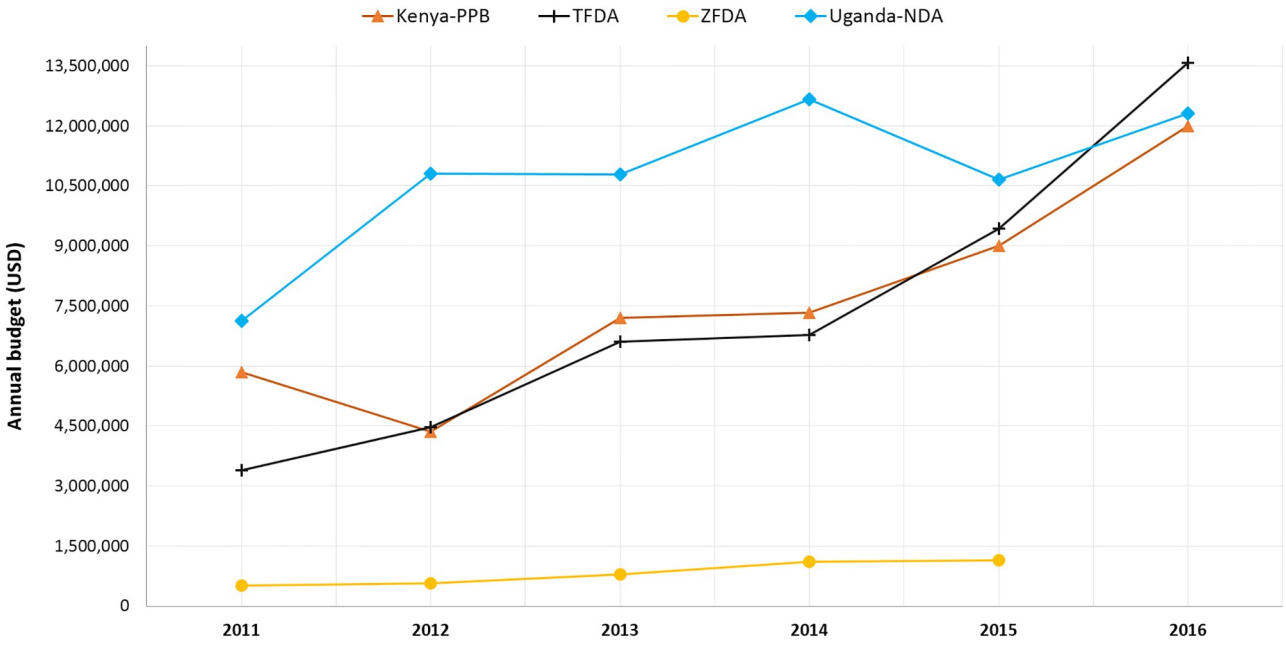

Fig 1. Trends in East African Community national medicines regulatory authorities' annual budgets.

https://doi.org/10.1371/journal.pone.0236332.g001

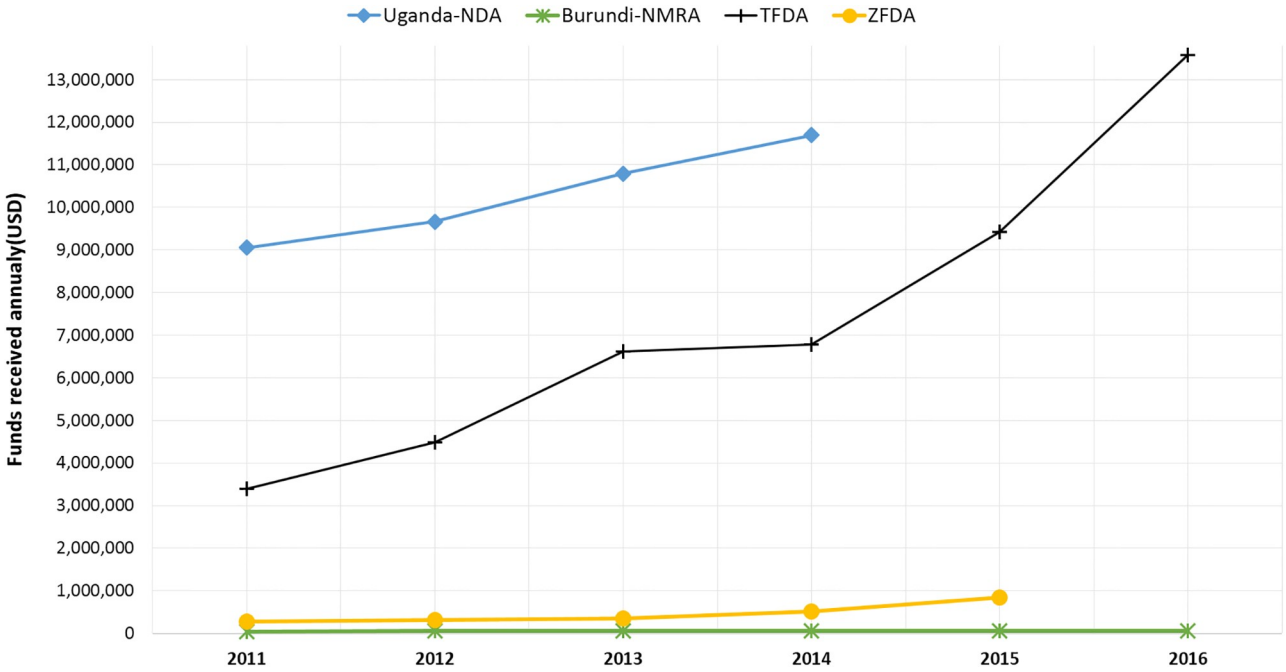

Fig 2. Trends in annual funding among national medicines regulatory authorities in the East African Community.

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Sources of revenue for NMRAs

Assessment of the various sources of funds received by the NMRAs indicated governments, industry fees, and donors to be the major funding sources across all NMRAs as shown in Fig 3. It should be noted that the PPB in Kenya only provided data on annual budgets without indicating the sources of its revenue. For the NMRAs in Tanzania-mainland (TMDA) and Uganda

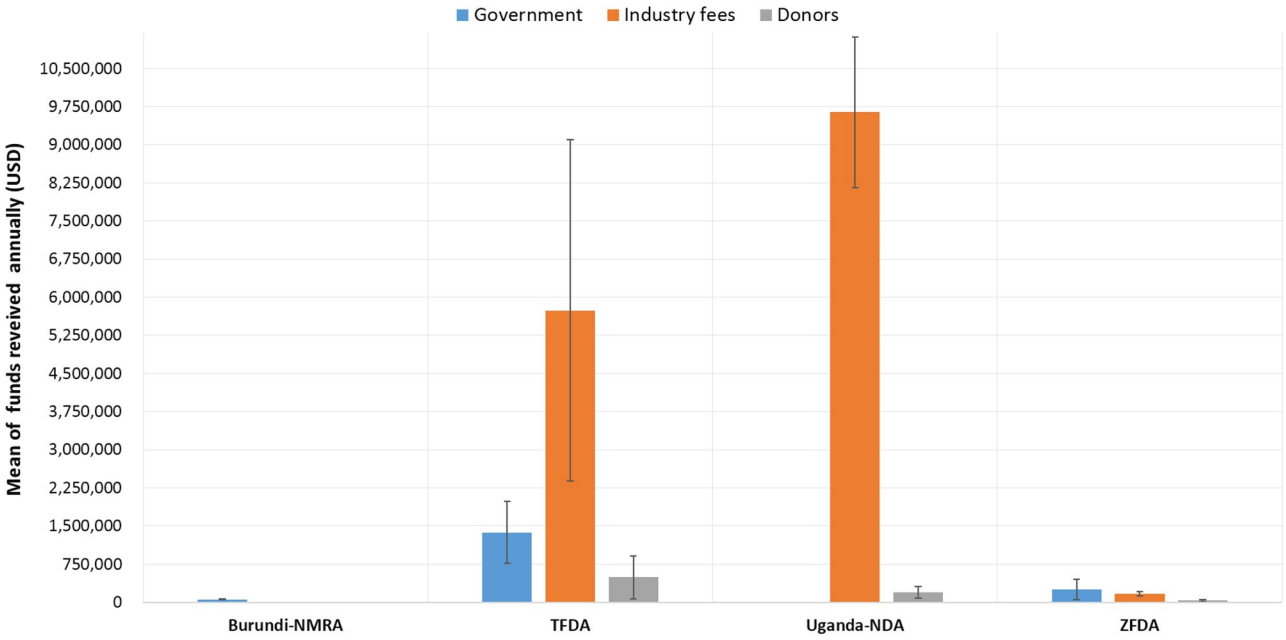

Fig 3. Annual mean amounts and sources of funds received by National medicines regulatory authorities.

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(NDA), industry fees were observed to be the major source of funds. On average, industry fees contributed up to 73.20% and 98.25% of the total annual revenue for TMDA NDA respectively. For Zanzibar (ZFDA) and Burundi NMRAs, the governments were observed to be the main sources of revenue with Burundi relying solely on the government funding while for ZFDA, on average government contributes 50.40%, industry fees 40.60% and the remaining 9% of the total revenue is from donors and other sources.

Funds received from donors indicated a high degree of variation, with some NMRAs receiving funding only once over a five years duration, while others received fluctuating amounts with no remarkable trends. Funding partners most cited include the Bill and Melinda Gates Foundation (BMGF), World Health Organization (WHO), United Nations Industrial Development organization (UNIDO), Clinton Health Access Initiative (CHAI), United Nations International Children's Fund (UNICEF), Management Sciences for Health (MSH), World Bank, Trademark East Africa Limited (TMEA), German Corporation for International Cooperation (GIZ), Global Fund, the United States Pharmacopoeia (USP) and the United States Agency for International Development (USAID) just to mention a few. On average, the overall contribution of funds received from donors by each NMRA was the least among other sources of financing.

NMRAs' expenditure

Observation of expenditure patterns indicated operational costs to be the major expense in the majority of the NMRAs, followed by salaries and infrastructure development as shown in Fig 4. This is also explained by the observed increase in the number of staff among the NMRAs from which the annual number of staff could be obtained (Fig 5). The PPB in Kenya indicated the highest degree of average expenditure across all three categories, with the least average expenditures being marked by the Burundi NMRA. Data from Rwanda and Zanzibar NMRAs were not available for this indicator. The operational costs on average increased considerably across all the NMRAs during the studied period.

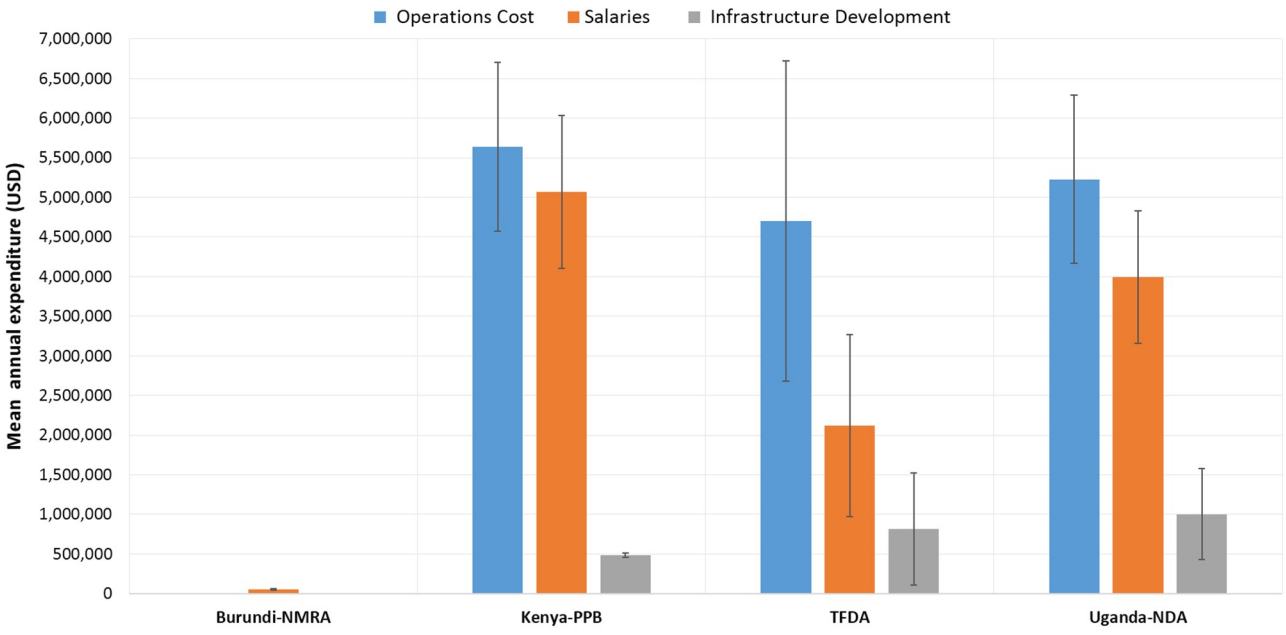

Fig 4. Mean annual amounts and main areas of expenditure by the national medicines regulatory authorities.

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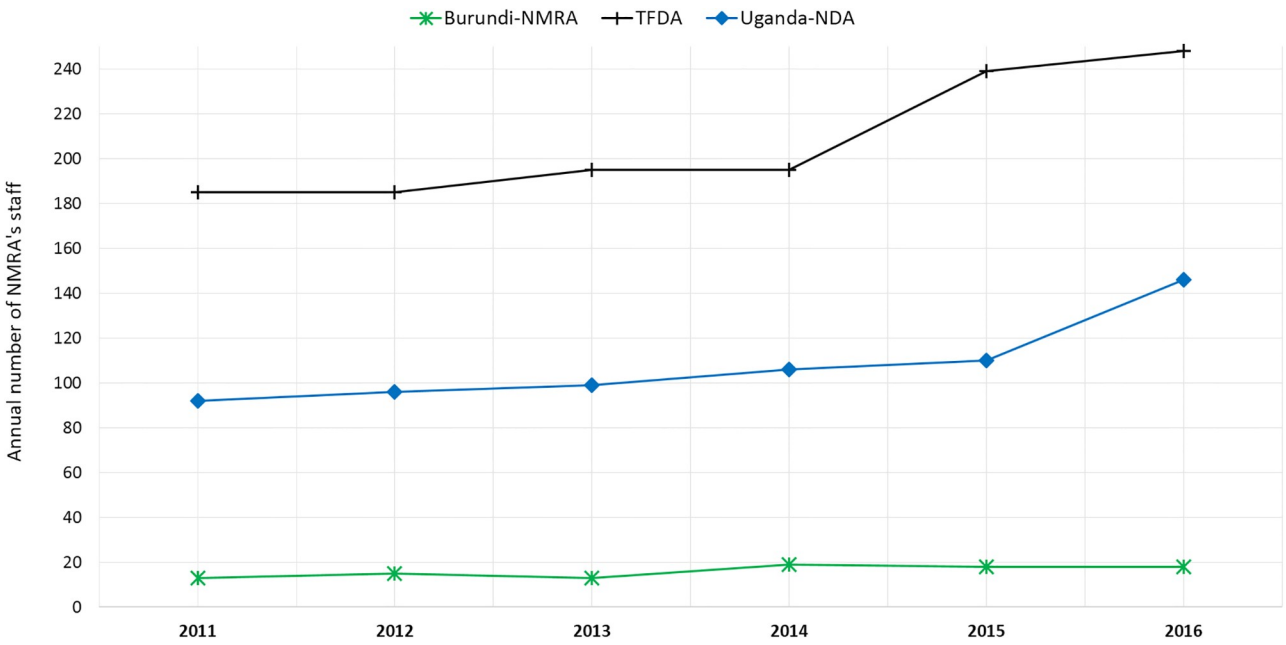

Fig 5. Annual trend in the number of staff per national medicines regulatory authority.

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Discussion

Clear government policy and legal framework to empower the NMRAs to collect and utilise fees for services offered is an essential element for sustainable funding [4]. Results from this study show that governments across the EAC region use different NMRA financing models to regulate pharmaceutical markets. While some rely entirely on government funding as is the case for Burundi NMRA, others use a combination of sources of revenue from government (50.40%), industry fees (40.60%) and donors and other sources (9%) as exemplified by ZFDA out of an average annual budget of USD 824,328.67. In the case of TMDA with the annual budget increasing from USD 3,384,123.00 to USD 9,422,888 and the contribution of industry fees to the total budget increasing over the years from 60% (USD 2,018,608.88) in 2011 to 86% (USD 8,123,093) in 2015, while the contribution from government has been steady at an average of 19.60% (USD 1,168,299.09) over the studied period. Yet, the government of Uganda largely depends on industry fees (98.25%, USD 8,077,238.20) to finance the NDA activities. The increase in revenue could be associated with the observed improvement in registration processes following the harmonization of registration systems and the introduction of quality management systems among the EAC Partner States [17].

Findings from this study are in agreement with the WHO multi-country study conducted in 2002 [4]. The WHO study reported a decrease from 100% to 60% donor funding between 1995 and 1997 in Uganda as the result changes in the NMRA funding policy, with the government and industry fees making up only 20% each. Currently, the Uganda NDA is 98.25% (USD 8,077,238.20) funded through fees for service with minimal contribution from donors. While there is no enough data for comparison with other EAC countries, the findings support the need for sound government policies and legal frameworks to empower the NMRA to collect and utilise fees as means to ensure financial sustainability [4].

In terms of an enabling environment for fees collection by the NMRAs, while the NMRAs in Kenya, Tanzania, Uganda, Rwanda, and Zanzibar have legal mandate to collect and utilise

fees, Burundi does not. Considering that medical products regulation is a public function, safeguarding funding for regulation of medical products against the competing needs of other government agencies is key for sustainability of NMRAs.

An alternative funding model is a combination of government budgetary allocation and industry fees, whereas the collected fees are transferred to the government central treasury as is the case for Malaysia and Venezuela [4]. This is in line with the study among Sub-Saharan African countries, which revealed that 35% of the NMRAs depend on government funding, with all fees paid directly to Treasury [5]. It has also been reported that the fees and charges are set arbitrarily and not necessarily linked to the cost of service provided while resource intensive services are offered free [4]. Therefore, for this model to be sustainable, the existing fees and other charges should reflect the real cost of services provided. Under such conditions, the NMRA can rely entirely on the charged fees to finance regulatory activities. In a situation where the collected fees are transferred to the government central treasury, the government must ensure that the funding allocation meets the budget requirement. While it is important that NMRAs are adequately financed to deliver on their mandate, attention should also be given on NMRAs expenditure to ensure accountability and balanced utilization of funds for public interest [4].

Another model is where the fees and charges reflect the real cost of services provided such as evaluation of dossiers and inspection of establishments, and the NMRA is financed entirely on fees for service as is the case with the Therapeutic Goods Administration (TGA) in Australia and Medicines Control Authority of Zimbabwe (MCAZ) which have full powers to use the revenue they collect [4]. The TGA in Australia is an example of an agency that moved gradually from government-financed to a self-financed agency through a government policy which was phased in over a five years period from 1994–1999. Industry fees, therefore, provide a reliable and sustainable source of revenue for NMRAs.

This is especially so as Africa witnesses convergence of changing economic profiles, rapid urbanisation, increased healthcare spending and investment, and increasing incidence of chronic diseases which is attributed to the USD 45 to 60 billion projection of the African pharmaceutical market by 2020 [6]. The increasing demand for medicines in Africa including the EAC region attributed by population and economic growth as well as raising consumer awareness warrants governments' investment on regulation of medical products [18].

Furthermore, governments investment in regional harmonization efforts and strengthening regulatory capacity and systems across NMRAs in the EAC partner states has a significant impact in improving availability of medicines through timely marketing authorization of essential medicines, reduced duplication of individual NMRAs efforts, streamlined use of limited resources with resultant savings in public health budgets [19,20]. This is exemplified by the EAC medicines regulatory harmonization program which has increased efficiency in registration processes among the NMRAs in the region with a subsequent reduction in registration timelines from the previous 1–2 years period to a median of 7 months [21].

In recognition of the need to ensure that all African citizens have access to safe, quality and efficacious essential medicines, the African Union approved the African Medicines Regulatory Harmonization (AMRH) Initiative as a key pillar of the Pharmaceutical Manufacturing Plan for Africa (PMPA) [22]. The AMRH Initiative which covers more than 85% of Sub-Saharan Africa serves as a foundation for establishment of the African Medicines Agency. AMA will build on the AMRH success through coordination of on-going regulatory systems and strengthening and harmonization efforts of the AU, RECs, Regional Health Organization (RHOs) and member States [23]. AMA also provides a good platform to support the ongoing African Continental Free Trade Area (AfCFTA)—anchored pharmaceutical project for the Small Island States (SIDS) and land locked countries including Seychelles, Madagascar,

Comoros, Mauritius, Djibouti, Eritrea, Rwanda, Ethiopia, Kenya, Sudan and IGAD. This pilot health and economic initiative established through public-private partnerships and innovative financing is intended to contribute to improved accessibility and affordability to safe medicines and to accelerated progress towards SDGs and Agenda 2063. All these initiatives provide an opportunity to invest in medicines regulation on the African continent.

Limitations of the study

In this study, data on population size, the number of pharmaceutical establishments and the pharmaceutical market size was intended to determine the level of investment (in terms of financial and human resources) required to control the market. However, only Burundi provided data on pharmaceutical market size making analysis and comparison between countries difficult.

It is also worthwhile noting another limitation in this study as a lack of information on the actual NMRAs fees structure which provides different streams of fees charged and how the funds collected are distributed in performing the different regulatory functions. A further study on fees charged by different NMRAs will provide useful information on fees structure and its basis as well as proportion of contribution from various streams of revenues.

Conclusion

Inadequate funding for NMRAs is one of the major challenges hampering effective regulation of medical products world-wide and within the East African Community. Measures are needed to guide countries to institute appropriate policies and legal frameworks which will ensure that NMRAs are empowered to collect and utilise fees for services they offer. Where the NMRA is not fully mandated and the market size does not provide enough financial resources for the NMRAs to perform their functions effectively, governments must ensure a dedicated budget is allocated to facilitate NMRA performance. Governments should also invest in NMRAs participation in regional harmonization efforts which have proven to facilitate effective and efficient utilization of already limited resources while at the same time reducing the time taken for applicants to put the product on the market.

There is a need to conduct further research to assess the fee structure employed by various NMRAs to determine whether it reflects the actual cost of service or not. The study can also explore the proportion of contribution from various streams of revenue and how they are allocated to support various regulatory functions and NMRAs participation in regional harmonization efforts. In addition, a study correlating population, pharmaceutical market size, with the level of investment needed to ensure effective market control needs to be conducted. This will assist in guiding governments on the level of investment needed for the NMRA in terms of infrastructure, financial and human resources, to ensure effective regulation of pharmaceutical market in a country.

Supporting information

S1 File. Questionnaire and checklist for heads of NMRAs and M&E experts.
(PDF)

S2 File. Indicators guidance notes.
(PDF)

S1 Table. Data.
(PDF)

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RESEARCH ARTICLE Open Access

Harmonization of medical products regulation: a key factor for improving regulatory capacity in the East African Community

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Abstract

Background: Limited capacity to regulate medical products is associated with circulation of products which do not meet standards of quality, safety and efficacy with negative public health and economic outcomes. This study focused on assessing the effect of the East African Community (EAC) medicines regulatory harmonization initiative on the capacity of national medicines regulatory agencies, with a focus on registration and inspection systems.

Methods: An exploratory mixed-method design using both qualitative and quantitative data to access data from six national medicines regulatory authorities (NMRAs) and the EAC Secretariat. Data was collected using a combination of semi-structured interviews, questionnaires, and checklists for the period 2010/11–2015/16 with 2010/11 data serving as baseline. Heads of NMRAs, regulatory and monitoring and evaluation experts, and the EAC Secretariat Project Officer were enrolled in the study. A set of 14 indicators grouped into 6 categories were used to assess NMRAs performance.

Results: Policy and legal frameworks provide a foundation for effective regulation. Collaboration, harmonization, joint dossier reviews and inspections of manufacturing sites, reliance and cooperation are key factors for building trust and capacity among NMRAs. Five out of six of the EAC Partner States have comprehensive medicines laws with autonomous NMRAs. All the NMRAs have functional registration and good manufacturing practice inspection systems supported by regional harmonised guidelines for registration, inspection, quality management and information management systems with four NMRAs attaining ISO 9001:2015 certification.

Conclusions: The EAC regulatory harmonization initiative has contributed to improved capacity to regulate medical products. The indicators generated from this research can be replicated for evaluation of similar initiatives across and beyond the African continent and contribute to public health policy.

Keywords: East African community, Medical products regulation, Regulatory capacity, Africa regulatory harmonization, Registration, Regulatory inspection, Efficiency, Governance

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Background

The African continent constitutes 15% of the world's population with a disproportionate disease burden of more than 25% [1, 2]. Africa's high disease burden and high mortality from preventable and curable diseases are partly due to inadequate health systems, scarce financial and human resources as well as unavailability of and unaffordable medicines that are of good quality, safe and efficacious [3]. Lack of access to quality, safe, efficacious and affordable medicines is in part attributed to limited local pharmaceutical manufacturing base and weak medicines regulatory systems [3]. In 2005 the Heads of State and Government of the African Union (AU) mandated formulation of the Pharmaceutical Manufacturing Plan for Africa (PMPA) with the view of strengthening Africa's ability to produce high quality and affordable medicines that will contribute to improved health and economic outcomes [4].

The coming into force of the African Continental Free Trade Area (AfCFTA) in 2019 serves as an impetus to boost intra-African trade through a single market of 1.2 billion people and a cumulative Gross Domestic Product (GDP) of over $3.4 trillion across the 55 member states of the AU [5, 6]. An estimated $259 billion health care and wellness sector by 2030 and the $45 billion projection African pharmaceutical market by 2020 are attributed to the changing economic profiles, rapid urbanization, increased healthcare spending and investment, and increasing incidence of chronic lifestyle diseases [7, 8]. The increasing demand of medicines in Africa due to population and economic growth as well as raising consumer awareness warrants governments' investment in local production and effective regulation of medical products [6, 9].

For many years the capacity to regulate medicines in Sub-Saharan African countries has been confronted with fragmented legal frameworks, weak management structures and processes, and a severe lack of staff and resources. This led to subsequent proliferation of substandard and falsified medicines in various markets [10, 11]. A report in 2010 revealed that 7% of the 46 sub-Saharan African countries have moderately developed medicine regulatory capacity, about 63% have minimal capacities and the remaining 30% have an NMRA in place [12]. Poor inspection practices, ineffective licensing and product registration systems, inadequate access to quality control laboratories, non-existent pharmacovigilance, clinical trials oversight and drug promotion control systems, with subsequent 30% product quality failure rates are characteristic of regulatory systems in Africa [13]. This is coupled with inadequate communication and information exchange systems, lack of transparency and accountability and conflict of interest. Another study conducted in 2017 revealed that except for Sahrawi Republic, the remaining African countries have NMRAs with varying organizational setups and levels of functionality, operating either as units or departments within Ministries of Health, or as semi- or fully autonomous agencies [14].

Governments and partners are called to build and strengthen medicines regulatory systems with appropriate legal frameworks and institutions so as to carry out regulatory functions while supported by mechanisms for collaboration among agencies [11]. Effective and efficient regulation of medical products provides an opportunity for investment in manufacturing, trade, and sale of pharmaceutical products, as well as an increase in research and development of new medical products and technologies. In turn, these yield social and economic benefits to the patients and communities at large [4, 13, 14]. Building medical products regulatory capacity is also crucial for achieving Universal Health Coverage (UHC) goals, the AU Agenda 2063 aspirations and goals 1 and 3, as well as Sustainable Development Goals (SDGs) on access to quality, safe and efficacious health products to the people [15].

The African Medicines Regulatory Harmonization (AMRH) Initiative is an attempt by the AU to strengthen regulatory capacity, encourage harmonization of regulatory requirements and expediting access to good quality, safe, and effective medicines [16]. The initiative is implemented as part of the AU's PMPA, a policy framework to provide an enabling regulatory environment for local production and contribute to the UHC, AU Agenda 2063 and SDGs goals [17, 18].

For the period between 2015 and 2016, countries in the East African Community (EAC) have recorded significant improvements in registration timelines from an average of 2 to 7 years to a median of 7 months [19, 20]. Within the *Zazibona*, the median timeline to product recommendation was 5 months in 2014 and 9 months for three consecutive years between 2015 and 2017. *Zazibona* is a collaborative procedure for registration of medicines initiated by Zambia, Zimbabwe, Botswana and Namibia in the Southern African Development Community SADC region.

The AMRH initiative is as well implemented in the Economic Community of West African States (ECOWAS), Intergovernmental Authority on Development (IGAD) and Economic Community of Central African States (ECCAS). It covers more than 85% of the Sub-Saharan African countries which are at different levels of its implementation. In order to address the problem of non-coherent medicines laws in African countries, the AMRH Initiative developed a Model Law on medical products regulation so as to ensure effective regulation and promotion of harmonization [20, 21]. The Model Law which among others promotes the establishment of autonomous agencies was adopted by the AU Assembly in January 2016 and has been domesticated by more

than 12 AU Member States. Since 2014, eleven regional centers of regulatory excellence have been designated since 2014 to provide coordinated and structured regulatory science training programmes using the existing academic institutions in partnership with regulatory agencies [20].

Understanding the relevance of various regulatory interventions undertaken at country, regional and continental levels is important for informing regulatory policy reforms undertaken by the AU, governments, and partners [22]. For this reason, this study was done to evaluate the effect of medicines regulatory harmonization initiative in the EAC region and to provide insights on whether it is making an impact on national regulatory capacity. We aimed at determining factors related to the improving regulatory capacity in the EAC NMRAs. Specifically; to determine the level at which countries have: i) Implemented agreed Common Technical Document (CTD) for registration of medicines in the EAC Partner States. ii) Implemented common Information Management Systems (IMS) for medicines registration in each of the EAC Partner States' NMRAs, and whether or not the IMS is linked in all Partner States and EAC Secretariat. iii) Implemented Quality Management Systems (QMS) in each of the EAC Partner States' NMRAs. iv) The level of capacity attained at regional and national levels in implementing medicines registration harmonization in the EAC region. v) Whether or not a framework for mutual recognition procedure has been developed and implemented among the EAC Partner States, and lastly vi) Whether or not a platform for information sharing with key stakeholders at national and regional level has been established. The hypothesis is that the EAC MRH Project implemented under the AMRH Initiative has increased regulatory capacity in the EAC Partner States.

Methods

Fourteen (14) indicators were developed and grouped into 6 main categories to ensure objective assessment of performance of regional medicines regulatory harmonization initiatives, as indicated in the indicators matrix (Table 1) [23]. Each indicator was further refined and validated to facilitate users' understanding, through validation workshops with monitoring and evaluation focal points from the EAC NMRAs, Regional Economic Communities (RECs) and the World Health Organization (WHO). The exercise aimed to ensure accuracy of data collected and to enable objective analysis.

Study design

In order to access data from six National Medicines Regulatory Authorities (NMRAs) and the EAC Secretariat, we employed an exploratory mixed-method design. We used Semi-structured interviews, questionnaires and checklists to gather data between 2010/11 and 2015/16, with 2010/11 data acting as the benchmark [24, 25]. During this period, both annual and three yearly data were gathered. A pilot situational analysis study informed the designing of the data collection tools [24, 26, 27]. In addition, we adopted other questions from the WHO Global Benchmarking Tool (WHO-GBT) for the Assessment of National Regulatory Frameworks [28]. We validated the data collection tools by pre-administering them some of the prospective respondents in all studied NMRAs.

During the first round of data collection, the Head and one monitoring and evaluation expert in each NMRA, as well as the project officer of the EAC MRH project responded to self-administered questionnaires and checklists [25]. We selected the respondents based on their roles and involvement in medicines policies and regulatory activities. The second round involved the conduction of semi-structured face-to-face interviews to one staff from medicines registration, GMP inspections, legal affairs, human resource and finance departments in addition to the previous set of respondents. One to two respondents were involved in each 1 to 2 h long interview session [24].

An acceptance letter and an interview subject guide were sent to the interviewees in advance. Moreover, we obtained a permission to record the responses in form of selected written notes from each respondent. Follow-up visits were carried out to capture the incomplete data and verify the previously obtained data. Confidentiality of all respondents was highly observed thought the study [24].

Data analysis

Qualitative data analysis and interpretation was carried out on all indicators involving the availability and corresponding details of the National policies, laws, guidelines, provisions, legal frameworks, level of autonomy, references and regulatory standards, GMP guidance and procedures as well as status of implementation of different modules. Qualitative data obtained using questionnaires, interviews and desk reviews of documents was organized, analysed and evaluated manually with the help of tables on MS Excel®.

On the other hand, quantitative data on aspects related to numbers of applications, joint assessments, products registered, timelines to registration of products, and number of NMRAs under a particular aspect were tabulated and analysed using MS Excel® for means, standard deviations, frequencies and proportions. Where only a single point/year data was provided by the respondent(s), it was reported as such. Due to lack of data from some agencies in some of the studied aspects, only the available data was used in statistical analysis.

Results

This publication is a continuation from a previous paper which looked at factors affecting financial sustainability

Table 1 Indicators Matrix

	Indicator Title	Type	Reporting Level	Frequency	Data Sources
Category 1	**Policy and legal framework**				
Indicator 1	National Medicines Policy (NMP)	Input	NMRA	Three yearly	WHO NMRA GBT, Government gazette, Ministry of Health
Indicator 2	Legal framework governing the regulation of medical products	Input	NMRA	Three yearly	WHO NMRA GBT, Government Gazette, National Law, Ministry of Justice library, NMRA records
Category 2	**NMRA governance**				
Indicator 3	NMRA level of autonomy	Output	NMRA	Three yearly	WHO NMRA GBT, CIRS OpERA programme, Government gazette, NMRA Financial report, Governance structure
Indicator 4	Availability of structures to support NMRA decision making process	Process	NMRA	Three yearly	NMRA Organisation/governance structure, Medicines law
Category 4	**Medicines evaluation and registration, and good manufacturing practice (GMP) inspection systems**				
Indicator 5	Availability of guidance and procedures for registration of medicines	Process	NMRA	Annually	WHO NMRA GBT, CIRS OpERA programme, NMRA records, Government policies and legislation
Indicator 6	NMRAs using regionally harmonized guidelines for product registration	Output	Regional	Annually	CIRS OpERA programme, NMRA Records; REC Records
Indicator 7	Availability of a process to track product registration applications and timelines	Process	NMRA	Annually	WHO NMRA GBT, CIRS OpERA programme, NMRA records
Indicator 8	Number of products applications with registration decisions per annum	Outcome	Regional	Annually	CIRS OpERA programme, NMRA records
Indicator 9	Proportion of NMRAs participating in joint assessments	Output	Regional	Annually	CIRS OpERA programme, REC records
Indicator 10	Proportion of product applications jointly assessed/ reviewed at regional level	Outcome	Regional; continental	Annually	CIRS OpERA programme, REC records
Indicator 11	Availability of a Good Manufacturing Practice (GMP) inspection guidance and procedure	Process	NMRA	Annually	WHO NMRA GBT, NMRA records, Government policies and legislation, WHO Assessment Reports
Category 5	**Functional Quality Management Systems (QMS)**				
Indicator 12	Implementation of Quality Management System (QMS) requirements by NMRA	Process	NMRA; regional	Annually	CIRS OpERA programme, NMRA QMS Records
Indicator 13	Percentage of NMRAs ISO 9001: 2015 Certification	Output	NMRA; regional	Annually	NMRAs QMS Records
Category 6	**Information Management Systems (IMS)**				
Indicator 14	Implementation of requirements for an integrated IMS	Output	NMRA; regional	Annually	WHO NMRA GBT, NMRA IMS

of NMRAs in the EAC region [24]. For the purpose of this paper, findings are categorised into five main categories namely policy and legal framework, NMRA governance, medicines registration and good manufacturing practice (GMP) systems, QMS and IMS.

Policy and legal frameworks

Progress has been observed in National Medicines Policies (NMPs) and Medicines Laws by the EAC Partner States as exemplified in Table 2. While only three countries indicated the availability of NMPs during the baseline study, currently all six countries have NMPs with a clear vision and indications for establishment of a semi- or autonomous NMRA. With respect to medicines laws, Tanzania-Mainland and Zanzibar amended their national laws in 2014 and 2016 respectively, while the Rwanda Food and Drugs Law was enacted in 2013 [29–34].

Governance

A baseline study revealed that, the Tanzania Medicine and Medical Devices Authority (TMDA), the Zanzibar Food and Drugs Board (ZFDB) and the Kenya Pharmacy and Poisons Board (PPB) were semi-autonomous entities, and that the head of the PPB also served as a Chief Pharmacist combining both regulatory and policy roles as the technical arm of the Ministry of Health. For Rwanda and Burundi,

Table 2 Status of indicators under policy and legal frameworks category (2010/11–2015/16)

	National Medicines Regulatory Agency					
	Burundi	**Kenya**	**Rwanda**	**Tanzania**	**Uganda**	**Zanzibar**
Indicator 1: National Medicines Policy (NMP)						
Availability of a National Medicines Policy (NMP)	Yes	Yes	Yes$^{\Delta}$	Yes	Yes	Yes$^{\Delta}$
Year of approval of the NMP by the Cabinet of Ministers	2012	2012	2016^{sd}	2007	2015	2014
Availability of a provision in the NMP for establishment of an autonomous national medicines regulatory agency (NMRA)	Yes	Yes	Yes$^{\Delta}$	Yes	Yes	Yes$^{\Delta}$
Existence of a vision for the NMRA	Yes	Yes	Yes$^{\Delta}$	Yes	Yes	Yes$^{\Delta}$
Policy comprehensiveness	Yes	Yes	Yes$^{\Delta}$	Yes	Yes	Yes$^{\Delta}$
Indicator 2: Legal framework governing the regulation of medical products						
Legal framework availability	Yes	Yes	Yes$^{\Delta}$	Yes	Yes	Yes$^{\Delta}$
Availability of a Law for regulating medicines in your country	Yes	Yes	Yes$^{\Delta}$	Yes	Yes	Yes$^{\Delta}$
Year of enactment of medicines law	1980	1957 (as amended in 2009)	2013	1978, (repealed 2003 and amended in 2004 & 2014)	1993	1986 (repealed in 2006 & amended in 2016)
Legislation comprehensiveness	No	–	Yes$^{\Delta}$	Yes	Yes	Yes$^{\Delta}$

NB: - = No data available/submitted; ^{sd} = Secondary data from the EAC MRH Project SC Meeting Report (2018); Yes$^{\Delta}$ = a change from No at baseline

the respective Ministries of Health Departments administered regulatory functions. Moreover, for the TMDA, PPB and the Uganda National Drug Authority (NDA), the agencies had powers to charge fees for regulatory services and received very little or no government subvention [26, 27].

Results have shown a significant improvement in the level of autonomy of the NMRAs. Currently, four NMRAs are operating as semi-autonomous agencies namely: the Rwanda Food and Drugs Authority (RFDA), TMDA, Zanzibar Food and Drugs Authority (ZFDA), and PPB; while NDA operates as a fully autonomous agency. Furthermore, the National Pharmaceuticals Regulation Law of Burundi was under consideration by the Burundian Parliament, provides for the establishment of a semi-autonomous NMRA to be called the Drug and Food Regulatory Authority of Burundi (ABREMA) [35]. Table 3 provides analysis of the NMRAs governance framework including the level of autonomy.

Moreover, there was a progressive trend in the development of regulations and guidelines among the EAC Partner States (Fig. 1). While baseline data showed three

Table 3 Status of indicators NMRA governance category (2010/11–2015/16)

	National Medicines Regulatory Agency					
	Burundi	**Kenya**	**Rwanda**	**Tanzania**	**Uganda**	**Zanzibar**
Indicator 3: NMRA level of autonomy						
NMRA's level of autonomy	Department within the Ministry of Health	Semi-Autonomous	Semi-Autonomous	Semi-Autonomous	Autonomous	Semi-Autonomous
Indicator 4: Availability of structures to support NMRA decision making process						
Medicine Law	Republic of Burundi. Decret No. 100/150 du 30 September 1980 portant Organization de l'exercise de la Pharmacie au Burundi. 1980.	Republic of Kenya. The Pharmacy and Poisons Act, Chapter 244. 1957, as amended in 2009.	Republic of Rwanda. Law No. 47/2012 of 14/01/2013 relating to the Regulation and Inspection of Food and Pharmaceutical Products. 2013	United Republic of Tanzania (Mainland). Tanzania Food, Drugs and Cosmetics Act, Cap 219. 2003, as amended in 2004, 2014 & 2019	Republic of Uganda. The National Drug Policy and Authority Act. 1993.	United Republic of Tanzania (Zanzibar). The Zanzibar Food, Drugs and Cosmetics Act. No. 2 of 2006 as amended in 2016
Existence of NMRA Governing Board	No	Yes	Yes	Yes	Yes	Yes$^{\Delta}$

NB: Yes$^{\Delta}$ = a change from No at baseline

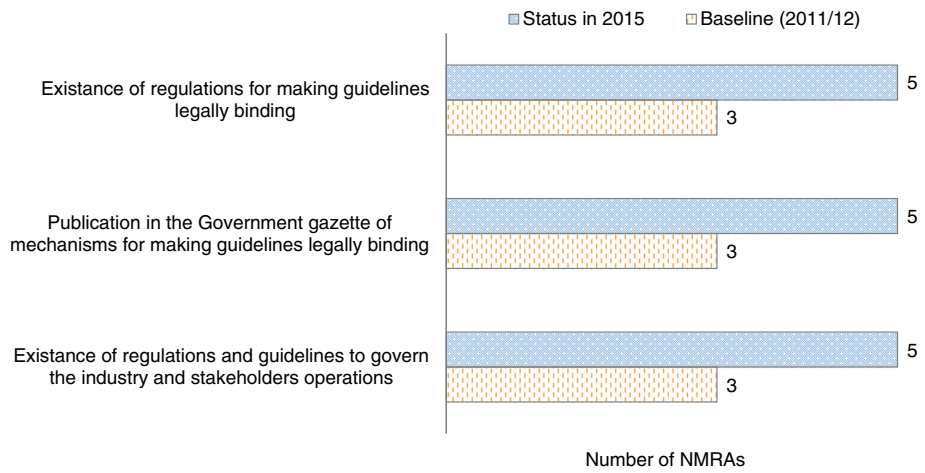

Fig. 1 Trends in developing regulations and guidelines (Indicator 4) in the EAC Partner States (excluding Burundi) (2011/12–2014/15)

out of the six NMRAs had regulations and guidelines, the end-line data, shows five out six NMRAs reported having regulations and guidelines in place.

Medicines registration system

Comparison of baseline data show improvement in registration systems in Rwanda and Burundi. All six NMRAs currently have a legal mandate to register medicines and a system to manage applications from receipt of a dossier to the issuance of a marketing authorization. In addition, all the NMRAs use the EAC harmonized guidelines for registration and Standard Operating Procedures (SoPs) for joint review of dossiers (Table 4). Also, all NMRAs participate in the EAC joint review of dossiers. However, the time taken to register a product based on the outcome of the joint review process still varies from country to country. For instance, out of fifteen applications received through the regional procedure, the TMDA registered all the products, whereas the proportion of products registered by other NMRAs was as shown in the brackets: PPB (13/15), Burundi (1/15), RFDA (9/15), ZFDA (1/15), and NDA (7/15) (Table 4). A reliance mechanism (where an agency relies on others in making a regulatory decision) exists in Kenya, Tanzania-Mainland, Tanzania-Zanzibar and Uganda while it was not the case for Burundi and Rwanda. Results on number of products applications received per annum (Table 4**,** under indicator 8) indicated the highest five years average of 800 new applications were received by the TMDA, followed by NDA (458), Burundi (70) and ZFDA (16). The PPB and RFDA indicated to have received 1030 and 833 applications respectively in 2016.

GMP inspection system

All six NMRAs have a legal mandate to conduct GMP inspection (Table 4, indicator 11). Except for Burundi NMRA, other NMRAs reported to be conducting inspections of manufacturing sites. While Kenya, Tanzania and Uganda NMRAs had conducted inspections since during the baseline study, Rwanda and Zanzibar NMRAs started in 2015. Moreover, All NMRAs indicated to be using the EAC harmonized guidelines for GMP inspection from 2015 when they came into force. Each NMRA reported having participated at least once in the EAC joint inspections. Additionally, the RFDA, NDA and ZFDA employ a reliance models by using GMP inspection reports from other agencies such as the EAC, Stringent Regulatory Authorities (SRAs), Pharmaceutical Inspection Convention (PIC), and the WHO Pre-Qualification Programme (WHO-PQ) (Table 4).

Functional quality management system

The International Standards Organization (ISO) certification is a globally recognized accreditation of the maturity and functionality of the QMS of an organization. The EAC MRH Projects advocates for implementation of QMS to facilitate delivery of quality and consistent services to customers. The NMRAs in Zanzibar, Burundi, Rwanda and Kenya had no QMS in place during baseline survey, the TMDA was ISO 9001:2008 certified and the NDA had initiated the ISO certification process. Evaluation of QMS implementation data from the EAC Partner States NMRAs indicated different levels of implementation as indicated in Table 5. However, currently the NMRAs in Kenya, Tanzania mainland, Uganda and Zanzibar are ISO 9001:2015 certified, while Rwanda and Burundi NMRAs are working towards the certification [36].

Functional information management systems

One of the objectives of the EAC MRH is to have all the Partner States' NMRAs implementing a common IMS

Table 4 Medicines Registration and GMP Inspection Systems in the EAC Partner States NMRAs (2011/12–2015/16)

	National Medicine Regulatory Agency					
	Burundi	**Kenya**	**Rwanda**	**Tanzania**	**Uganda**	**Zanzibar**
Indicator 5: Availability of guidance and procedures for registration of medicines						
Legal mandate to register medicines	Yes	Yes	Yes	Yes	Yes	Yes
Availability of a system for receiving applications, evaluating and providing marketing authorisation for medicines	Yes	Yes	Yes	Yes	Yes	Yes
Indicator 6: NMRAs using regionally harmonized guidelines for product registration						
Availability and use of EAC Harmonized guidelines for registration of medicines	Yes$^{\Delta}$	Yes$^{\Delta}$	Yes$^{\Delta}$	Yes$^{\Delta}$	Yes$^{\Delta}$	Yes$^{\Delta}$
Year EAC Harmonized Guidelines for Registration of Medicines came into force	2015	2015	2015	2015	2015	2015
Indicator 7: Availability of a process to track product registration applications and timelines						
Availability of mechanism for tracking registration timelines	No	Yes (2011)	No	Yes (2011)	No	Yes (2015)
Average timelines range attained for Fast-tracked products	–	3 months	–	4–6 months	–	–
Average timeline range attained for normal review	–	12 months*	–	12 months*	–	12 months*
Indicator 8: Number of products applications with registration decisions per annum (Mean ± SD)						
Applications received per annum	70.0 ± 42.0	1030*	833*	799.7 ± 275.2	457.80 ± 148.73	16.00 ± 18.89
Application carried over from previous reference year(s)	0.0 ± 0.0	1000*	575*	443.0 ± 301.4	–	0
Medicines registered by the NMRA per annum	0.0 ± 0.0	514*	175*	463.0 ± 224.6	344.40 ± 243.87	6.20 ± 4.76
Indicator 9: Proportion of NMRAs participating in joint assessments						
Participation in EAC joint assessments	Yes (2015)	Yes (2015)	Yes (2015)	Yes (2016)	Yes (2015)	Yes (2015)
Number of joint assessments participated by NMRA	1	1	1	3	1	3
Existence of policy on abridged procedure for registration of medicines	No	No	No	Yes (2011)	Yes (2016)	No. It is happening but there is no written policy yet.
Reference regulatory standard used on abridged procedure for registration of medicines	None	WHO-PQ	EAC & WHO-PQ	In-house SOP	EAC, SRAs & WHO-PQ	WHO-PQ
Indicator 10: Proportion of product applications jointly assessed/ reviewed at regional level						
Number of products registered based on EAC joint dossier review[sd]	1/15	13/15	9/15	15/15	7/15	1/15
Time taken to register medicines based on joint review outcome[sd]	–	–	–	–	–	–
Indicator 11: Availability of a Good Manufacturing Practice (GMP) inspection guidance and procedure						
Legal mandated to conduct GMP inspection	No	Yes (2011)	Yes (2015)	Yes (2011)	Yes (2011)	Yes (2015)
NMRA using EAC Harmonized guidelines for good manufacturing practice (GMP) inspections	No	Yes (2015)	Yes (2015)	Yes (2015)	Yes (2015)	Yes (2015)
Year EAC GMP inspection guidelines came into force	–	2015	2015	2015	2015	2015
Participating in EAC joint GMP inspections	Yes (2014&16)	Yes (2015)	Yes (2015)	Yes (2015)	Yes (2012)	Yes (2012)

Table 4 Medicines Registration and GMP Inspection Systems in the EAC Partner States NMRAs (2011/12–2015/16) *(Continued)*

	National Medicine Regulatory Agency					
	Burundi	**Kenya**	**Rwanda**	**Tanzania**	**Uganda**	**Zanzibar**
Availability of policy on GMP assessment of pharmaceutical manufacturing sites using document review	No	No	Yes	No	Yes	No (it is happening but there is no written policy yet)
Reference regulatory standard used for GMP document review	–	–	EAC, PICs & WHO-PQ	–	EAC, WHO-PQ, US-FDA, EMA, PICS Inspection Reports	EAC GMP inspection report, WHO-Prequalification GMP inspection reports-

NB: Year in the bracket indicating the time from which the indicator started to apply; Yes$^{\Delta}$ = a change from No at baseline; * = only 2015/16 data (not average); – = No data available/ submitted; ^{sd} = Secondary data from the EAC MRH Project SC Meeting Report (2018)

for medicines registration, which is linked in all Partner States and the EAC Secretariat. A robust IMS is key for supporting the technical aspects of medicines regulation, to facilitate efficiency and effectiveness of business processes, improve transparency, facilitate decision-making process, sharing and exchange of information among NMRAs and stakeholders, and timeliness of approval of registration decisions. During the baseline survey, the TMDA had an integrated system which was locally developed whereas the PPB used SIAMED®. The NDA, on the other hand, used a combination of SIAMED®, ACCESS® and a locally developed software. Burundi had a manual IMS, which was not functioning, ZFDA had a functional manual registry and Rwanda had both a manual and an electronic system. The method of capturing information in NMRAs in the EAC Partner States was variable and unreliable. The electronic systems were not user friendly, difficult to integrate with other IMS platforms, could not automatically generate or print certificates or be linked to websites. The existing manual systems were labour intensive.

A comparison of IMS implementation status with baseline data shows a significant improvement in all countries, with Burundi and Zanzibar moving from manual to electronic systems. All the EAC NMRAs are currently using a harmonized IMS whereby four out of five NMRAs reported sharing regulatory information amongst each other as indicated in Fig. 2 and Table 6.

Discussion

The current environment of increased globalization imposed by the geo-economic-political situation warrants an advocacy for cooperation and harmonization among NMRAs across the world as basis for building and strengthening regulatory capacity. This is especially important given the fact that harmonization initiatives support regulators' mandate to promote and protect public health when backed with clear governance structures and regulatory frameworks [37].

Medicines policies and laws serve as the foundation for effective regulation of medical products. A comparative study of medicines laws in the EAC region revealed that medicines laws exist in all EAC Partner States with varying legal provisions, key regulatory functions, and practices. These potentially affect availability of good quality, safe and efficacious medicines needed on the market [35]. In order to ensure effective regulation of medical products, convergence of regulatory practices through streamlining the existing legal frameworks is essential [35]. In this regard, it is important for countries to consider domestication of the AU Model Law on Medical Products Regulation which has the necessary provisions for a country to have a robust regulatory system such as core regulatory functions (as recommended by WHO), some level of autonomy, NMRA's participation in harmonization initiatives and collaboration with other agencies. The increased advocacy under the EAC MRH Project has helped in creating awareness on the part of policy makers and politicians on the importance of investing in medical products regulation with subsequent improvement in policy and legal frameworks in all the countries of the EAC region.

Regulatory harmonization facilitates pharmaceutical companies' submission of a single set of the dossier to several different countries with subsequent reduction of costs. Harmonization processes are also beneficial for

Table 5 Status of the Quality Management System in the EAC Partner States NMRAs (2011/12–2014/15)

	National Medicine Regulatory Agency					
	Burundi	**Kenya**	**Rwanda**	**Tanzania**	**Uganda**	**Zanzibar**
Indicator 12: Implementation of EAC QMS in the NMRA based on ISO-9001 standard	No	Yes (2011)	No	Yes (2014)	Yes (2014)	Yes
Indicator 13: ISO-9001 Certification of NMRA medicines regulatory system	No	No	No	Yes (2010)	No	No

NB: Year in brackets indicates the time from which the indicator started to apply

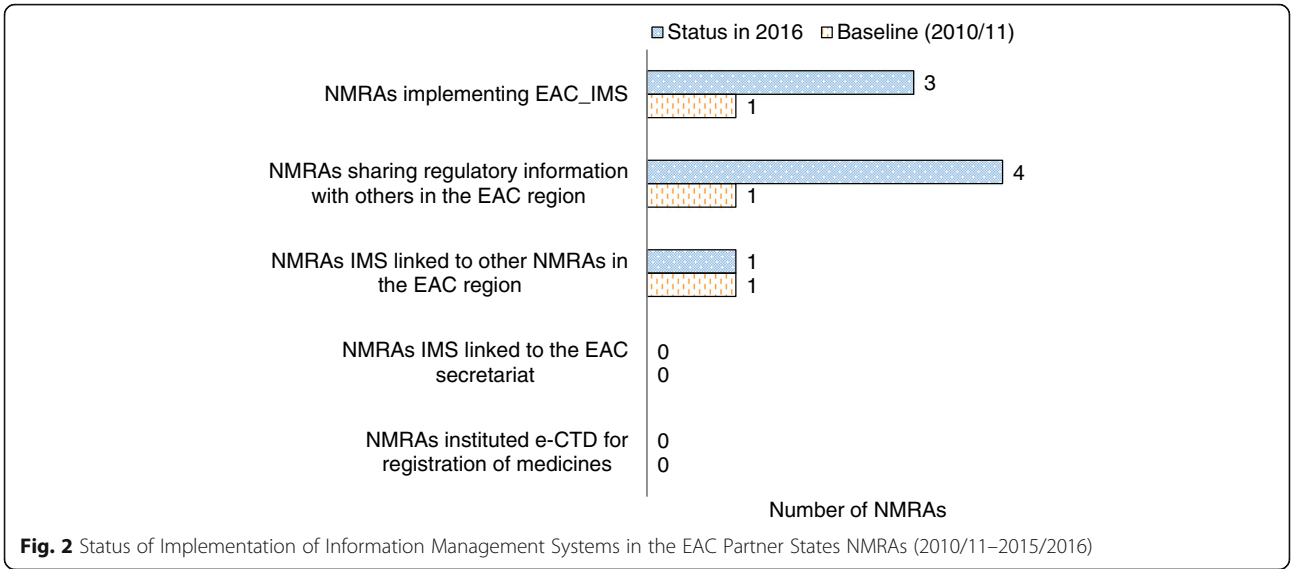

Fig. 2 Status of Implementation of Information Management Systems in the EAC Partner States NMRAs (2010/11–2015/2016)

public health as they facilitate open-minded technical discussions and the exchange of ideas and experience among regulators from different countries [38]. The EAC regulatory harmonization experience has enhanced regulatory science by increasing the rigour of the review process, with subsequent higher quality standards than national procedures. In turn, this has reduced the overall regulatory burden and led to less duplication of efforts [36, 39, 40]. These contribute to the strengthening of the capacity of the NMRAs in expedition of the assessments of priority medicines and filtering out of substandard or falsified products [38]. Sound, efficient, effective and transparent regulatory systems are as well important for the promotion of investment in pharmaceutical sector and socioeconomic advancement [11].

The decision to harmonise guidelines for registration of medicines and GMP inspections in the EAC region has simplified the process for manufacturers intending to lodge an application in any of the countries [59]. In addition, reliance mechanisms for registration of medicines employed by PPB, TMDA, ZFDA and NDA; reliance mechanisms for GMP inspection implemented by RFDA, NDA and ZFDA; and appropriate governance mechanisms to support sound and timely regulatory decisions by NMRAs are attributed to the improved efficiencies observed in these countries. For example, there has been a considerable improvement in the NMRA governance frameworks with a subsequent establishment of autonomous agencies in Kenya, Tanzania mainland, Rwanda, Uganda and Zanzibar.

The attainment of ISO certification by NMRAs is another factor that can be related to improved regulatory efficiency. With a resultant increase in the number of received applications as observed in Kenya, Tanzania

Table 6 Status of implementation of different key modules by the NMRAs under Information Management Systems (IMS) category in by 2015

	National Medicine Regulatory Agency						
	Burundi	**Kenya**	**Rwanda**	**Tanzania**	**Uganda**	**Zanzibar**	**EAC Secretariat**
Indicator 14: Status of key modules in Implementation of requirements for an integrated IMS							
Premises	✓	✓	✓	✓	✓	✓	×
Products	×	✓	✓	✓	✓	✓	×
GMP	✓	✓	✓	✓	✓	✓	×
Inspection	×	✓	✓	✓	✓	✓	×
Import and Export	×	✓✓	✓✓	✓	✓✓	×	NA
Finance Module	✓✓✓	✓✓✓	✓	✓✓✓	×	×	NA
Report Module	✓✓✓✓	✓✓✓✓	✓✓✓✓	✓✓✓✓	✓✓✓✓	✓✓✓✓	✓✓✓✓

Key: ✓ = fully functional; ✓✓ = fully functional and integrated to National Revenue Authority; ✓✓✓ = fully functional and integrated to e-banking and/or Mobile money; ✓✓✓✓ = fully functional and reports customized according to the national and regional needs; × = non-functional; NA = not applicable (Source: EAC Secretariat MRH Project Progress Report, 2015

mainland and Uganda. The ISO certification will also increase confidence in the quality of NMRAs work, increasing trust and facilitate reliance on registration and inspection processes as viewed by peer agencies in the region and across the continent [36]. It is important to note that ISO certification of the NMRAs is one of drivers of a robust medicines regulatory system. Similar means in place include being ranked by the WHO – GBT for evaluation of national regulatory systems. This was demonstrated by the TMDA by achieving the WHO – Maturity level 3 in 2018, becoming the first African NMRA to do so [41]. According to the WHO, the attainment of Maturity level 3 indicates that an agency has a stable well-functioning and integrated system of oversight for medical products. Further, it is of essence to recognise the progress made by the PPB, NDA and ZFDA, considering they had no QMS in place during the baseline survey. Rwanda is moving toward the attainment of the ISO 9001:2015 certifications while the NMRA in Burundi implemented quality objectives and standard operating procedures for some regulatory activities, including medicines evaluation and registration [36].

Furthermore, an operating IMS that links all Partner States is essential for improving efficiency as it assists the EAC Secretariat and NMRAs in tracking the progress of applications in their own as well as neighboring countries. All EAC Partner States now have a functioning IMS, and it is agreeable that this has boosted efficiency and strengthened cross-departmental linkages. The IMS platforms are designed to allow as many processes as possible to be conducted online through a single portal, whereby the PPB is the only agency which allows the electronic submission of dossier applications. Implementation of the EAC Cooperation Framework agreement also requires IMS platform for NMRAs to communicate and share information [36].

Harmonization initiatives are not spared of challenges. One of the challenges experienced by the EAC harmonization initiative is the unfamiliarity with regulatory systems of other NMRAs. This resulted into a lengthy process from development of harmonized guidelines to the actual coming into force in January 2015. The process involved eleven steps to familiarise all the key stakeholders such as regulators and industry with new guidelines and entailed additional costs for sensitization and training [40, 42]. Experience shows that sometimes countries are unwilling to commit to a uniform code due to differences in political economy and ethical systems. In a situation where there are differences in legal frameworks, it may imply that definitions of terms among countries are different ("generic", "reference product", "data exclusivity", "pharmacopoeia", "variations", etc.) hence causing delays in the harmonization process. Medicines acceptable for market authorizations by the NMRAs as well as acceptable indications may also vary between countries based on differences in treatment guidelines and therapeutic traditions. Other challenges include differences in technical requirements, for example bioequivalence (BE) requirements for complex products and differences in aspects related to product and Active Pharmaceutical Ingredients (API) (e.g. source, method of manufacture and packaging). Moreover, divergence following joint approval due to separate handling of post-approval changes, variations in assessment timelines based on regulations and differences in data exclusivity/patent rules, are other factors to be well considered when implementing harmonization initiatives [40].

Although some countries have proven to be faster than others in granting marketing approval of products following the regional review process, many applicants are hesitant to use the joint product assessment procedure until efficiency improvements are made. While it has been reported that the regional procedure is of unexpectedly higher quality standards than national procedures, a common frustration is the time taken to receive the actual marketing authorization especially for smaller, less attractive markets [39]. These differences may be due to the diverse nature of governance (whether autonomous agency with its own Board or a department under the Ministry of Health) and execution of roles among the NMRAs, as well as the existence of non-streamlined policies, laws and guidelines in the respective countries. There is a need to further study factors hampering national uptake of joint review process as they affect marketing authorization timelines. Improvements are therefore required for the current EAC processes to meet the vision of harmonization.

Key performance indicators developed as part of this study have helped to identify gaps in the regional harmonization process. While the baseline assessment tool focused on the national regulatory system, legal framework, marketing authorization and regulatory inspection, the indicators tool developed during this study provided more insights into the interactions between NMRAs. These are mainly through regional processes like implementation of regional harmonised guidelines, execution of joint regulatory activities and subsequent uptake of the outcomes of the regional joint review and inspection processes.

Harmonizing regulatory standards across countries, work and cost-sharing arrangements, collaboration between NMRAs, as well as advocacy and information campaigns are key aspects in addressing the existing regulatory limitations in and across countries. The AMRH provides a platform to support RECs, Regional Health Organizations (RHOs) and Member States, in harmonizing medicines regulation with a view to build

and strengthen regulatory capacity. These are achieved through mobilizing interested governments, donors and other stakeholders to invest in medicines regulation [18, 29]. The AMRH Initiative also serves as a foundation for the establishment of the African Medicines Agency (AMA) as enshrined in the AU Executive Council Decision EX.CL/872(XXVI) of January 2015 [20, 43]. It is expected that these initiatives will accelerate research and development of new or improved medical interventions for Poverty-Related Neglected Diseases (PRNDs), provide an enabling environment for local manufacturing, and contribute towards the AU Agenda 2063 and the global 2030 SDGs [18, 20].

Way forward for the initiative

Review of the EAC MRH Project in 2017 identified three key challenges including limited access to public information about the process; limited information flow from regulators to industry during the joint assesment process; and a significant lag time between a joint assessment recommendation and national registration decisions.

As a result of these challenges, the EAC Partner States came up with a package of solutions. First, the NMRAs of the Partner States agreed on a cadre of Regional Technical Officers (RTOs) who are responsible for the day-to-day management of joint activities and recommending programmatic changes to the initiative's Steering Committee. The Partner States also agreed on implementing the Cooperation Framework Agreement for the NMRAs, as also approved by the EAC's Council of Health Ministers in May of 2018. This serves as an intermediary step toward a binding mutual recognition agreement between all Partner States. The cooperation framework will facilitate implementation of joint assessment or inspection decision and ensure that regulatory decisions are made in a timely manner and honoured throughout the region. On funding the Initiative, the region will introduce a framework for contributions from the Partner States' NMRAs. This includes a coordination fee to support regional assessment and inspection processes to complement donor funding. The long-term goal is to establish a semi-autonomous EAC Medicines Agency which will ensure that the program continues to grow and improve [44].

The process of widening the scope of medical products has started with harmonization of regulation of in vitro diagnostics (IVDs), and medical devices with a view to include vaccines, biologics and biosimilars. Regulatory activities will also be expanded to cover clinical trials oversight, safety and quality surveillance initiatives. Furthermore, the initiative has welcomed the South Sudan's new NMRA towards addressing the regulatory challenges as the youngest member of the EAC [44].

Study limitations

Missing some of the data from some of the NMRAs led to the lack of a complete regional picture in several aspects of this study.

Conclusion

The improved operational efficiencies with subsequent faster and more consistent review and approval process is a result of the regulatory harmonization, which has facilitated faster availability of products in the EAC market. It is expected that regulatory and product development costs will decrease and the industry submission practices will be aligned with fewer parallel registrations. Moreover, the resultant mutual learning and consistency in applying international guidelines for registration of medicines or inspection of manufacturing sites are anticipated.

The study has shown improved regulatory capacity in the EAC Partner States at varying degrees and timelines. The EAC Partner States have strived to put in place comprehensive policies and legal frameworks to support regulation of medical products with subsequent use of harmonised regional guidelines. Quality management system and information management systems have shown to be necessary tools for improving efficiency of regulatory processes. Moreover, the improved work-sharing through shared knowledge and skills among NMRAs has resulted in faster regulatory approvals and improved availability of safe, efficacious, and good quality medicines.

The developed indicators tool serves as basis for evaluation of regulatory harmonization networks on the African continent and beyond. We expect that the gaps identified, and lessons learnt from using the indicators tool in this study can be used as basis to refine it for further use.

Abbreviations

ABREMA: *Autorite' Burundaise de Regulation des Medicaments et des Aliments* (Drug and Food Regulatory Authority of Burundi); AfCFTA: African Continental Free Trade Area; AMA: African Medicines Agency; AMRH: African Medicines Regulatory Harmonization; API: Active Pharmaceutical Ingredient; AU: African Union; BE: Bioequivalence; CTD: Common Technical Document; EAC: East African Community; ECCAA: Economic Community of Central African States; ECOWAS: Economic Community of West African States; GDP: Gross Domestic Product; GMP: Good Manufacturing Practice; IGAD: Intergovernmental Authority on Development; IMS: Information Management System; ISO: International Standards Organization; IVDs: In vitro Diagnostics; NDA: National Drug Authority; NMPs: National Medicines Policies; NMRA: National Medicines Regulatory Authority; PIC: Pharmaceutical Inspection Convention; PMPA: Pharmaceutical Manufacturing Plan for Africa; PPB: Pharmacy and Poisons Board; PRNDs: Poverty-Related Neglected Diseases; QMS: Quality Management Systems; RECs: Regional Economic Communities; RFDA: Rwanda Food and Drugs Authority; RHOs: Regional Health Organizations; RTOs: Regional Technical Officers; SDGs: Sustainable Development Goals; SRAs: Stringent Regulatory Authorities; TMDA: Tanzania Medicine and Medical Devices Authority; UHC: Universal Health Coverage; WHO: World Health Organization; WHO-GBT: World Health Organization Global Benchmarking Tool; WHO-PQ: World Health Organization Pre-Qualification Programme; Zazibona: Zambia, Zimbabwe, Botswana and

Namibia; ZFDA: Zanzibar Food and Drug Authority; ZFDB: Zanzibar Food and Drugs Board

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Authors' contributions
MS was responsible for the study conception design of the work, acquisition, analysis, interpretation of data for the work and initial drafting of the report. NB and NN were responsible for data collection while NEM did data analysis and provided critical revision of the manuscript. MJ, NS and EK provided critical revision of the manuscript including analyses, interpretation of data and final approval of the version to be published.

Authors' information
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Availability of data and materials
All relevant data are within the manuscript. The data collection instruments, and the datasets used during the current study are available from the corresponding author upon request.

Ethics approval and consent to participate
Ethics approval was granted by the WITS Human Research Ethics Committee on 31st July 2015 through clearance certificate No. M150751. Furthermore, ethical clearances and approval were granted by the Medical Research Coordinating Committee of the National Institute for Medical Research in Tanzania (NIMR/HQ/R.8a/Vol.IX/2184), the Scientific and Ethics Review Unit of the Kenya Medical Research Institute (KEMRI/RES/7/3/1), the Ministry of Public Health and AIDS Control in Burundi; the Ministry of Health in Rwanda (No20/5545/DGCPHS/PH/2015), the Ministry of Health in Uganda, the Ministry of Health of the Revolutionary Government of Zanzibar (BD.301/366/01), and the East African Community Secretariat (PSS/2/4/13). Moreover, informed consent forms were signed by individual respondents from NMRAs in the EAC Partner States and the EAC Secretariat.

Consent for publication
Not applicable.

Competing interests
Authors have declared that no competing interests exist.

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7. ANNEXES

ANNEX 7.1: INFORMATION SHEET FOR PARTICIPANTS

Good day;

My name is Margareth Ndomondo-Sigonda. I am a PhD student at University of the Witwatersrand, Department of Pharmacy, Pharmacology and Therapeutics, Faculty of Health Sciences. I am conducting a research project titled 'Evaluation of Medicines Regulatory Interventions in East African Community region" focusing on medicines registration harmonization (MRH) and WHO Prequalification Programmes. I am inviting you to participate in this study, which is a survey using a self-administered questionnaire; because I believe that you can provide important insights on medicines regulation and other interventions in your region and how your county is participating in the Programmes under the East African Community.

What is the purpose of this study?

The study will assess the extent to which EAC Partner States have benefited from the MRH and WHO-PQP Programmes. I will look at the existence of regulatory policies, legal frameworks and the EAC regional harmonised guidelines developed under the MRH Programme and procedures and how they are implemented at country levels and further assess the financial and human resources capacity of the NMRAs in the region.

Specifically, this research will determine the extent to which EAC Partner States have; i) implemented an agreed common technical document for registration of Medicines; ii) implemented a common information management system for medicines registration in each on the NMRA's which are linked in all Partner States and EAC Secretariat; iii) implemented a quality management system in each of the EAC Partner States' NMRAs; iv) built regional and national capacity to implement medicines registration harmonization in the EAC; v) developed and implemented a framework for mutual recognition based on Chapter 21, Article 118 of the East African Community Treaty; vi) created a platform for information sharing on the harmonized Medicines registration system to key stakeholders at national and

regional level. It will also explore how the WHO-PQ Programme has contributed to strengthening regulatory capacity in the region.

You are one of 3 respondents at national level selected by me and all your inputs for this self-administered questionnaire will be kept confidential.

Why have you been invited to take part?

You have been invited to take part because of your involvement in medicines regulatory matters and your substantial experience in the field. I believe that you will provide insightful views on how you see regulation of medicines in the EAC region.

What procedures are involved?

I will ask you to answer a questionnaire that will be e-mailed to you, that explores your views on medicines regulation and harmonization interventions in the East African Community Partner States. The study involves a questionnaire survey and/or interviews to respondents who participated in the questionnaire survey and who have agreed to participate in a more in-depth interview. You may indicate now if you wish to participate in this aspect of the study which will be done later.

Do you have to answer this questionnaire?

No. You can refuse to answer this questionnaire. Even if you agree, you can change your mind at any time. Your non-participation or withdrawal from this study will not prejudice you in any way.

What are the risks of taking part in this questionnaire?

You may worry that I am testing you on how much you know about management effectiveness. This is not the case. Rather, I hope to establish the existence or non-existence of regulatory capacity in the EAC Partner States with a view to inform policy makers on the appropriate interventions to be taken and provide recommendations on how best the existing resources (financial and/or human) can be utilised.

What are the benefits?

It is possible that taking part in the study will assist in generating new knowledge in the field of medicines regulation within and outside the country and contribute to

informing policy organs on how best NMRAs can be managed and supported by Governments and development partners.

What will happen to the data and how will confidentiality be maintained?

All data will be kept confidential. Only grouped data will be reported upon, so identification of individuals' viewpoints cannot be done. Your name and other identifying details including the questionnaire data will be stored safely, that is, in a locked cabinet, and electronic records will be password protected. The data will be kept in storage in de-identified form and not destroyed.

What will happen to the results?

Results will be included in my PhD Thesis, academic publications in open access journals; conference presentations and also as part of report back to all the participants.

What do you need to do?

If you agree to participate, I will need you to sign the informed consent form below and return the self-administered questionnaire to me. The questionnaire will take about 15 to 30 minutes. If you need to discuss any questions you may have about the study, please contact me. This may be in person or over the phone or email. You may also want to indicate your willingness to participate in the follow-up in-depth interviews and you can do so by placing the X in the appropriate box in the declaration form attached.

Will participants be paid?

Persons who take part in this survey will not be paid.

Was this study ethically approved?

This study proposal was approved by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand. In addition, ethical clearance has been sought from Kenya Medical Research Institute (KEMRI); Tanzania National Institute for Medical Research (NIMR); Ministry of Public Health and AIDS Control, Burundi; Ministry of Heath, Rwanda; Ministry of Health, Revolutionary Government of Zanzibar; and East African Community Secretariat.

Who can I contact if I have questions?

For questions related to the study, please contact me Margareth Ndomondo-Sigonda at +27 83 563 6250 or email me at 766425@students.wits.ac.za. You can also contact my supervisors; Dr. Jacqui Miot, on Jacqui.mot@wits.ac.za and Prof. Shan Naidoo on Shan.Naidoo@wits.ac.za. If you have questions about your rights as a participant, you may contact Prof. Peter Cleaton-Jones at the University of the Witwatersrand, Human Research Ethics Committee Secretariat on +27 (0)11 717 1234.

Furthermore, you can contact the following national ethics committees, Ministries of Health in your country and regional authorities:

Burundi, Permanent Secretary, Ministry of Public Health and AIDS Control, Tel: +257 22 242 542

Kenya: KEMRI Ethics Review Committee, P.O. Box 54840-00400, Nairobi, Tel: +254 (020) 2722 541, 07222 05901, 0733 400003, and 07177 19477; e-mail: seru@kemri.org.

Rwanda: Permanent Secretary, Ministry of Health, Tel: +257 22 242 542

Tanzania (Mainland): Chair, MRCC, NIMR, P.O. Box 9653, Dar es Salaam; Tel: +255-22-2121400; e-mail: hqs@nimr.or.tz;

Tanzania (Mainland): Permanent Secretary, Ministry of Health, Revolutionary Government of Zanzibar, P.O. Box 236, +255-21-22 33454, e-mail: afyasmz@zanlink.com

East African Community: Secretary General, P.O. Box 1096, Tel: +255 27 21 621 100/14, e-mail: eac@eachq.org

Please note that by filling in and returning the questionnaire you are in fact giving consent to participate in this survey. I will appreciate if after filling the questionnaire is sent back to me at 766425@students.wits.ac.za.

I, _____ _____ (full names of participant) hereby confirm that I have been informed by the researcher, Margareth Ndomondo-Sigonda, about the nature, conduct, benefits and risks of the study. I have also received, read and understood the written information sheet. I hereby give permission for data collected to be used for this PhD Research.

SIGNATURE OF PARTICIPANT: _____

DATE: _____

ANNEX 7.2: QUESTIONNAIRE AND CHECKLIST

This detailed survey for NMRA provides an overview of the regulatory system in a country including existing capacities and limitations and participation in the East African Community medicines regulatory harmonization scheme. Please fill in the required information and place a tick or a cross in your answer to the questions below:

CATEGORY	**YES**	**NO**	**N/A**
POLICY AND LEGAL FRAMEWORK			
Policy Framework			
Is access to quality, safe and efficacious medicines one of the priority components of a national health delivery system?			
Is there a national medicines policy (NMP) in the country? (Yes or No)			
If Yes; when was the NMP approved by the Government? (Indicate year of approval)			
Does the NMP provide for establishment of an autonomous national medicines regulatory agency (NMRA)? (Yes or No)			
Legal Framework			
Is there a Law for regulating medicine in your country? (Yes or No)			
What is the name of the law regulating medicines in the country? Mention:……			
When was the medicines law enacted? Indicate year:……			
Indicate if the following provisions and functions are covered in the legislation			
Market Authorization			
Licensing Manufacturers, Importers, Exporters, Wholesalers and Distributors			
Post Market surveillance and safety monitoring			
Regulatory Inspection and Enforcement			
Control of Clinical Trials of Medical Products			
Control of Promotion and Advertisement of Medical Products			
Establishment of Quality Control Laboratory			
Scheduling, Classification and Control of medical products			
Prohibition of Substandard/Spurious/Falsified/Falsely-labelled/Counterfeit (SSFFC) medical products			

Control of narcotics and psychotropic substances			
Scope of regulated products			
Offences and legal proceedings			
Administrative appeal procedures			
International Cooperation and Harmonization of Regulation of Medical Products			
Monitoring and Evaluation of National Regulatory Systems			
Transparency and information sharing			
Monitoring and evaluation of regulatory systems			
Power to make regulations			
Number and type of Regulations made under the Act			
Specified Guidelines to be made under the Act			
Declaration and Conflict of interests			
Restriction of liability			
Protection of and access to information			
Regulation of other related products			
Commencement and entry into force			
GOVERNANCE, MANAGEMENT AND FINANCING			
NMRA Governance			
Is the NMRA autonomous? Yes of No			
Is there a Governing Board for NMRA? Yes or No			
If Yes, indicate if the Board is Strategic, Executive or Advisory in its nature of functions			
Are there Technical/Expert Committee(s) responsible for assessing applications for registration of pharmaceutical products and GMP inspection? (Yes or No).			
Who makes the final registration decision? (Tick as appropriate)	Yes	No	
Board			
Technical/Expert Committee			
Other (specify)			
Indicate frequency of Technical Committee and Board meetings per annum (p.a.)	<2 p.a.	2-4 p.a.	> 4 p.a.
Board			
Technical/Expert Committee on Registration of medicines			

Technical/Expert Committee on GMP Inspection			
NMRA Management			
Quality Management System (QMS) in EAC			
Has the NMRA instituted the EAC QMS (Yes or No)			
If Yes, is the NMRA registration processes ISO Certified (Yes or No)			
Management Information System (MIS) in EAC			
Has the NMRAs instituted the EAC-MIS (Yes or No)			
Is the NMRA sharing regulatory information with others in the EAC region (Yes or No)			
Is the NMRA MIS linked to other NMRAs in the EAC region (Yes or No)			
Is the NMRA MIS linked to EAC Secretariat (Yes or No)			
Has the NMRA instituted e-CTD for registration of medicines (Yes or No)			
Communication			
Does the NMRA have a Website? (Yes or No)			
If Yes, provide the URL address:			
Are documents made available on the website? (Yes or No).			
If Yes, indicate below the type of documents posted on the website:			
Medicines Policy			
Medicines Law			
Regulations			
Guidelines			
Fees Structure			
List of registered products			
List of rejected products			
List of banned products			
List of licenced establishments (manufacturers, importers, wholesales/distributors, retailers, others)			
Other documents (specify)			
Regulatory Policies (regulations, guidelines, circulars e.t.c)			
What are the existing regulations, guidelines and circulars relating to regulation of medicine in your country? Please provide the name and the date they came into force on a separate sheet			
Are there procedures for making guidelines legally binding? (Yes/No).			
If Yes, please indicate the type of procedure used:			

Publication in Government Gazette			
Regulations			
Other (specify)			
Stakeholders Involvement			
Is there a mechanism for engaging key stakeholders in instituting regulatory policies (Yes or No)			
If Yes, indicate category of stakeholders involved			
Pharmaceutical industry			
Researchers/Scientists			
Academia			
Parliamentarians			
Civil Society Organizations (CSOs)			
General Public			
Other (specify)			
What mechanism is used for engaging stakeholders?			
Meetings			
Workshops			
Seminars			
Other (elaborate)			
Is/are there National Association(s) of Pharmaceutical Industry (Yes or No)			
If Yes, indicate the category of associations Pharmaceutical Manufacturers' Association Pharmaceutical Traders' Association Other (specify)			
Is there a mechanism for assessing the level of customer satisfaction with services offered by the NMRA? (Yes or No)			
If Yes; explain how: …… ……			
NMRA FINANCING			
What is the total annual budget (in US$) for the NMRA and financing gap for the past five (5) years?			
2011			
2012			

2013			
2014			
2015			
What are the sources of funding for the NMRA in US$? If possible, please indicate the approximate % by source for the last 4 years.			
Government			
Industry Fees			
Donors			
Other (please specify)			
Is the regulatory authority allowed to retain service fees collected from industry for execution of regulatory functions? Yes/No/Partly.			
If Yes or Partly; provide explanation how is the money used: …… ……			
Is the NMRA Audited annually (Yes or No)			
If Yes, indicate audit outcome for the past five (5) years (e.g. unqualified, qualified or adverse opinion)			
2011			
2012			
2013			
2014			
2015			
MEDICINES REGISTRATION & GMP INSPECTION SYSTEM			
Pharmaceutical Industry Size			
What is the size of pharmaceutical industry in value (US$)? Please indicate figures over the past 5 years: 2011:…… 2012:…… 2013:…… 2014:…… 2015:……			
What is the size of pharmaceutical industry by establishments? Please indicate numbers in each category and year *Manufacturers:* 2011:……			

2012:…… 2013:…… 2014:…… 2015:……			
Wholesalers/Distributors: 2011:…… 2012:…… 2013:…… 2014:…… 2015:……			
Retailers: 2011:…… 2012:…… 2013:…… 2014:…… 2015:……			
Health Facilities (Hospitals; Health Centres and Dispensaries) 2011:…… 2012:…… 2013:…… 2014:…… 2015:……			
Registration System			
Does the NMRA conduct registration of medical products? (Yes or No).			
Does the NMRA use the EAC Harmonized guidelines for registration of medicines? (Yes or No)			
When did the EAC Harmonized Guidelines for Registration of Medicines come into force in your country?			
Is the NMRA participating in EAC joint assessments (Yes or No)			
If Yes to above, indicate the # of joint assessments participated in 2015			
Does the NMRA have a policy on abridged procedure for registration of medicines (Yes or No)			
If Yes, what is the reference regulatory standard used (Tick as appropriate)			
Decision by other NMRAs in the EAC region			

EAC joint assessment report			
WHO-Prequalification product assessment reports			
US-Food & Drug Administration (US-FDA) product assessment reports			
European Medicines Agency (EMA) product assessment reports			
Other (specify)			
It there a policy on registration timelines(Yes or No)			
Is there a fast track policy for registration of medicines? (Yes/No)			
If Yes, what type of medicines are considered high-priority (tick as appropriate)			
HIV/AIDS drugs			
TB drugs			
Malaria drugs			
Cancer drugs			
Other (Specify)			
Does the NMRA institute a policy for waiver of registration requirement for certain categories of products? (Yes or No)			
If Yes, indicate categories of medicines under waiver mechanism			
GMP Inspection System			
Does the NMRA conduct inspection of manufacturing sites? (Yes or No)			
Does the NMRA use EAC Harmonized guidelines for good manufacturing practice (GMP)? (Yes or No).			
When did the EAC GMP guidelines come into force in your country?			
Is the NMRA participating in EAC joint inspections? (Yes or No)			
If Yes, indicate the # of EAC joint inspections participated in 2015			
Does the NMRA have a policy on abridged procedure for inspection of medicines (Yes or No)			
If Yes, what is the reference regulatory standard used (Tick as appropriate)			
Decision by other NMRA in the EAC region			
EAC GMP inspection report			
WHO-Prequalification GMP inspection reports			
US-FDA GMP inspection reports			
EMA GMP inspection reports			
GMP Inspection based on Pharmaceutical Inspections Convection Scheme (PICS) Member Inspection Reports			

Other (specify)			
Product Applications, Review and Monitoring Capacity			
How many product applications have been received per annum over the past 5 years?			
2011			
2012			
2013			
2014			
2015			
What is the total # of products registered by the NMRA annually over the past five years?			
2011			
2012			
2013			
2014			
2015			
What is the total # of products registered by NMRA annually using regionally agreed guidelines in 2015?			
New drugs			
HIV/AIDS (ARVs)			
TB			
Malaria			
Cancer drugs			
Other			
# of products registered by the NMRA based on joint assessments and GMP inspections			
# of products given marketing authorization based on abridged procedure e.g. EAC NMRA, WHO-PQ or SRA processes			
Is there a mechanism for monitoring registration timelines (Yes or No)			
If Yes to above, indicate average timelines (with %) attained for registration of different priority medicines			
New drugs			
HIV/AIDS drugs			
TB drugs			
Malaria drugs			

Cancer drugs			
Other (Specify)			
NMRA HUMAN RESOURCE			
Number of Staff and Qualification			
What is the total number of staff in the NMRA and their qualification?			
Pharmacists			
Medical Officers (Doctors)			
Veterinary Surgeons			
Chemists/Analysts			
Pharmaceutical/Laboratory technicians/Assistants			
Lawyers/Legal Experts			
Accountants			
Human Resource Officers			
Procurement Officers			
Administration Staff			
Other (specify)			
Please provide human resources distribution by qualification, roles and responsibility in product evaluation and GMP inspection:	Product assessors	GMP inspectors	
Pharmacists			
Medical Officer (Doctor)			
Veterinary Surgeons			
Chemists/ Analysts			
Pharmaceutical / Laboratory technicians/ Assistants			
Other (Specify)			
Are regulatory decisions purely based on internal scientific assessment? (Yes or No).			
If No; indicate the number and area of external expertise used outside NMRA.	Type of Expertise	# of expertise	
Evaluation of quality data			
Evaluation of Safety data			
Evaluation of efficacy data			
Lead GMP Inspectors			
Experts in QMS			

Experts in MIS			
Experts in other areas (specify)			
National and Regional Human Resource Development Plans			
Is there a human resource development plan for the NMRA? (Yes or No)			
If Yes, indicate the % implementation of the plan (# of staff planned to be trained vs # actually trained) in the past 5 years for evaluators and inspectors?	Product assessors	GMP inspectors	
2011			
2012			
2013			
2014			
2015			
Does the NMRA participate in regional training programmes organized under the EAC Harmonization Scheme? (Yes or No)			
If Yes, indicate the number of staff trained and the type of training attained in the EAC regulatory training programmes in the table below:	Type of Training	# Staff Trained under EAC Project	
Medicines registration			
GMP inspections			
EAC-QMS			
EAC-IMS			
Does the NMRA provide experts (trainers) to train staff under the EAC Harmonization Scheme? (Yes or No)			
If Yes, indicate the number of trainers and the area of specialization in the table below:	Type of Training	# of Trainers	
Medicines registration			
GMP inspections			
EAC QMS			
EAC IMS			
Other regulatory fields in the NMRA (specify)			
Indicate how many NMRA staff have participated in WHO-PQ Training programme over the past five years from 2011-2015, the type of training and the level attained (trainee or Lead) by filling in the table below:	Trainee	Lead	
Medicines assessor (Quality)			
Medicines assessor (safety)			

Medicines assessor (efficacy)			
GMP Inspector			
Other (specify)			
Indicate (in a separate sheet) how many NMRA staff have over the past five years from 2011-2015, participated in training programmes organized by other partners, the type of training and the level attained by filling in the table below:	# of staff trained	Level of Qualification Attained	Name of Organization(s) supporting the Training Programme
Short-Courses (btn 2 – 24 weeks):			
Product Registration & Evaluation			
GMP Inspection			
QMS			
IMS			
Other (specify)			
Medium-Term Courses (btn 25 – 48 weeks):			
Product Registration & Evaluation			
GMP Inspection			
QMS			
IMS			
Other (specify)			
Long-Term Courses (>12 months)			
Product Registration & Evaluation			
GMP Inspection			
QMS			
IMS			
Other (specify)			
PARTNERSHIPS AND COORDINATION			
Are there development partners and/or international organizations providing financial support to NMRA? (Yes/No)			
If yes, provide in a separate sheet names of development partners and international agencies providing support to NMRA on various regulatory functions/mechanisms at country level			
Medicines Registration			
GMP inspection			
QMS			

IMS			
Other (specify)			
What is the reporting procedure for programmes funded by partners?			
NMRA Procedure			
Government procedure			
Partners Procedure			
Other (Specify)			
Is there a mechanism for coordination of partners providing support to NMRA? (Yes or No)			
If Yes, elaborate below:			
NMRAs Partners Forum			
Ministry of Health Partners Forum			
Other (Specify)			

ANNEX 7.3: INDICATORS GUIDANCE NOTES

Guidance to indicators measurement: The matrix below provides indicator title, purpose, rationale for selecting the indicators, method of measurement[1], measurement frequency and unit of measurement, sources, indicator classification, data type and institution responsible for reporting on the respective indicators.

CATEGORY 1: POLICY AND LEGAL FRAMEWORK
Indicator 1: National Medicines Policy (NMP)2
a) Purpose: The indicator assesses whether the country has a current National Medicines policy (NMP) and if the available policy is comprehensive in line with WHO recommendations.
b) Rationale: National Medicine Policy expresses and prioritizes the medium- to long-term goals set by the government for the pharmaceutical sector and identifies the main strategies for attaining them. The policy is aimed at promoting equity and sustainability of the pharmaceutical sector. The general objectives of a national medicines policy are to ensure; I) access; ii) quality; and iii) rational use of medicines. Specifically, the policy ensures; equitable availability and affordability of essential medicines (access); the quality, safety and efficacy of all medicines (quality); the promotion of therapeutically sound and cost-effective use of medicines by health professionals and consumers (rational use); and increase the national pharmaceutical production capacity. A national medicines policy expresses the commitment to a goal and a guide for action.
c) Method of measurement: Availability, comprehensiveness and how current a policy[3] is will be determined responses three parts: 1) Availability of a National Medicines Policy (NMP) 2) Comprehensiveness of the NMP will focus on the following key components as recommended by WHO[4]: - Availability of a section of essential medicines - Affordability of these essential medicines - Availability of medicines financing - Availability of supply system - Existence of local manufacturing - Availability of Regulations and Quality Assurance - Availability of a Provision in the NMP for Rational use - Availability of a Provision in the NMP for Research - Availability of a Provision in the NMP for Human Resource

[1] AMRH data collection tool to be administered to (respondents is attached as an annex (1)
[2] **RS03.01:** A national medicines policy, aligned with health policy, exists and is implemented. Current policy means a policy that has been reviewed within 5 years.
[3] Current policy means a policy that has been reviewed within 5 years.
[4] http://apps.who.int/medicinedocs/documents/s19583en/s19583en.pdf

- Availability of a Provision in the NMP for monitoring and evaluation - Availability of a Provision in the NMP for establishment of an autonomous national medicines regulatory agency (NMRA) - Existence of a vision for the NMRA 3) Year of last review or amendment of the policy by the Cabinet of Ministers
d) Evidence/ Sources: WHO NRA GBT, Government gazette, Ministry of Health
f) Institutional Responsibility: Ministry of Health
g) Measurement frequency: Three yearly
h) Unit of measurement: Yes/ No
i) Data Type: Qualitative
j) Indicator Classification: Input
Indicator 2: Legal framework governing regulation of medical products5
a) Purpose: This indicator assesses whether a country has a legal provision governing regulation of medical products or not, and its comprehensiveness based on the AU Model law.
b) Rationale: One of the challenges in ensuring effective regulation of medical products in Africa is the existence of numerous gaps in legal provisions in Member States. Also, the existing legal provisions in most countries vary in comprehensiveness and do not have clauses enabling NMRAs to utilise decisions made by others in the region nor internationally. The gaps and differences in legislation are a major hurdle in harmonization at the regional level. The *African Union Model Law on Medical Product Regulation* thus provides a systematic approach in the review and development of national legislation that will enable Member States to undertake their obligation to protect the health of their people. The purpose of the African Union Model Law is to provide a comprehensive guide to countries as they review or develop national laws to facilitate regulatory systems strengthening and harmonisation.
c) Method of measurement: Availability of a Law for regulating medicine in your country is assessed by: 1) Availability of a Law for regulating medicine in your country and the year of enactment of medicines law 2) Comprehensiveness of the law will be assessed based on the following elements as defined in the African Union Model Law on Medical Product Regulation: - *Establishment of a body responsible for medicines regulation*

[5] **WHO NBT Sub Indicator RS01.01**: Legal provision and/or regulation defines the medical products and technologies that need to be regulated.

- *Availability of licensing of Manufacturers, importers, exporters, distributors and retailers/ dispensing outlets* - *Availability of Market authorization/ Registration of medicines* - *Availability of inspection of premises and manufacturing sites* - *Establishment of Quality Control Laboratory* - *Control of clinical trials* - *Control of Substandard/ Spurious/ Falsified/ Falsely labelled/ counterfeit (SSFFC) medicines* - *Scheduling, classification and control of medical products* - *Post-marketing Surveillance and Safety monitoring of products* - *Control of product promotion and advertisement* - *Control of other products* - *Control of narcotics and psychotropic substances* - *Offences and legal proceedings* - *Administrative appeals procedure* - *Authority to make regulations and guidelines* - *International cooperation* - *Regulatory Harmonization* - *Mechanism for assessing the level of customer satisfaction with services offered by the NMRA* - *Monitoring and evaluation of national regulatory system*
d) Evidence/ Sources: WHO NRA GBT, Government Gazette, National Law, Ministry of Justice library, NMRA records
e) Institutional Responsibility: NMRA, Ministry of Health
f) Measurement frequency: Three yearly
g) Unit of measurement: Yes/ No
h) Indicator Classification: Input
i) Data Type: Qualitative
CATEGORY 2: NMRA GOVERNANCE
Indicator 3: NMRA level of autonomy 6
a) Purpose: This indicator assesses the level of autonomy of an NMRA
b) Rationale: One of the key challenges on regulatory systems strengthening in most countries in Africa is the absence of an autonomous7 National

[6] **WHO NBT Sub Indicator RS02.04**: Independence of NRA from researchers, manufacturers, distributors and wholesalers, as well as the procurement system.

Medicines Regulatory Authority mandated to regulate the market. In countries where regulatory functions are split among two or more agencies, there is usually duplication of efforts, lapses in implementation, inconsistencies and spreading of limited resources too thinly. The AU Model Law provides for the establishment of autonomous NMRAs for effective coordination and regulation of medical products in a country.
1) **Method of measurement:** NMRA level of autonomy is assessed by the level of autonomy of the NMRA indicating either of the following: - Fully autonomous - Semi-autonomous - Department under the Ministry of Health *2) If autonomous, respondent indicate the following:* - *Ability to generate and utilise revenue* - *NMRA decision making power* - *Ability of NMRA to recruit staff*[8] - *Ability of NMRA to sue or be sued*
c) Evidence/ sources: WHO NRA GBT, CIRS OpERA programme, Government gazette, NMRA Financial report, Governance structure
d) Institutional Responsibility: NMRA, Ministry of Health
e) Measurement frequency: Three yearly
f) Unit of measurement: Yes/ No
g) Data Type: Qualitative
h) Indicator Classification: Output
Indicator 4: Availability of structures to support NMRA decision making process
a) Purpose: This indicator assesses the availability of structures and processes to support NMRA decision making as outlined in the AU Model Law on Medical Product Regulation
b) Rationale: NMRA decision making structures and processes are important for supporting evidence-based decision-making process within the NMRA. Regulatory decisions made by the NMRA must be informed by sound technical and scientific evidence provided by technical committees. The existence of an NMRA Board a strategic advisory structure is also important for ensuring transparent processes in regulatory decision making.

[7] According to WHO, Autonomous Agency means a financially and operationally independent body from other government bodies but accountable to the public

[8] **WHO NBT Sub Indicator RS06.01:** The NRA has the power to select and recruit its own staff following documented procedures based on its own written criteria (experience, minimum educational background, advanced training, etc.).

Furthermore, the existence of an appeals committee is important to avail applicants that are not satisfied with decisions made by the NMRA, an opportunity to appeal.
c) Method of measurement[9]: Existence of structures to support NMRA decision making process is assessed by 1) **Existence of:** - The board - The head of agency - Technical committee - Administrative Appeals Committee
d) Evidence/ Sources NMRA Organisation/governance structure, Medicines law
e) Institutional Responsibility: NMRA
f) Measurement frequency: Three yearly
g) Unit of measurement: Yes/No
h) Data Type: Qualitative
i) Indicator Classification: Process
CATEGORY 3: NMRA FINANCING
Indicator 5: Level of NMRA funding
a) Purpose: The total funding means the money that has been received each year by the NMRA and includes all sources such as government funding, fees for services rendered, income from investments, partner funding etc.
b) Rationale: Limited funding for National Medicines Regulatory Authorities (NMRA) is one of the major challenges hampering regulatory systems in most African countries. Financial capacity of any NMRA has a direct impact on its performance and growth. Population is a proxy for the size of the pharmaceutical market which will determine the level of investment required to control the market. This indicator therefore contributes to the understanding of the ability of the NMRA to regulate the market.
c) Method of measurement: The indicator is calculated as total funding for NMRA (in USD) as a proportion to the population each year. Secondary data on population from official government sources forms the denominator for the indicator. - **Numerator:**Total annual funding for the NMRA - **Denominator:** Population of the country

[9] Users to consider organization and governance indicators of the GBT as proxy indicators

d) Unit of Measurement: Proportion
e) Measurement frequency: Annually
f) Evidence/ Sources: CIRS OpERA programme, NMRA records, Ministry of Health
g) Indicator Classification: Input
h) Data Type: Quantitative
i) Institutional Responsibility: NMRA; Ministry of Health
Indicator 6: Reliability of NMRA funding
a) Purpose: This indicator assesses the ability of an NMRA to sustain its activities using the revenue generated from various sources and government subvention.
b) Rationale: NMRAs funding comes from several sources including government subvention, revenue from services rendered and investments as well as donations. The ability of the NMRA to generate and utilise own revenue is critical for strengthening and sustaining its ability to control the market. Furthermore, considering that medical products regulation is a public function, it is anticipated that government substantially supports NMRAs.
c) Method of measurement: Indicator 6 is calculated using two methods: 1) Financial sustainability measured by assessing trend on annual income over expenditure over study period based on fees for service and government subventions against donor funding. 2) Total revenue generated by NMRA (in USD) as a percentage of the total NMRA funding[10] (in USD) each year. NMRA revenue includes revenue from services rendered and investments. - Numerator Total NMRA revenue generated by NMRA X 100 - Denominator Total NMRA funding 3) Total government[11] funding for NMRA (in USD) as a percentage of the total NMRA funding (in USD) each year - Numerator: Total government funding for the NMRA X 100. - Denominator: Total NMRA funding
d) Evidence/ Sources: Central Medical Stores financial records, Ministry of finance records, approved annual national budget, NMRA: CIRS OpERA programme, Central Medical Stores records, Ministry of finance records, Approved annual national budget, NMRA records

[10] Total funding means the money that has actually been received in a given year by the NMRA and includes all sources such as government funding, fees for services rendered, income from investments, partner funding etc.
[11] Total government funding is the money actually received by NMRA from the government including operational costs and staff salaries.

e)	**Institutional Responsibility:** NMRA; Ministers of Health; Ministry of Finance
f)	**Measurement frequency:** Annually
g)	**Unit of Measurement:** Percentage (%)
h)	**Data Type:** Quantitative
i)	**Indicator Classification:** Input
CATEGORY 4: MEDICINES REGISTRATION AND GOOD MANUFACTURING PRACTICE (GMP) INSPECTION SYSTEMS	
Indicator 7: Availability of guidance and procedures for registration of medicines	
a)	**Purpose:** This indicator assesses the availability of a system for receiving applications, evaluating and providing marketing authorisation for medicines. The indicator focuses on assessing the availability of core components of a medicines registration system[12] in a country.
b)	**Rationale:** Medicines registration systems is an important component of the pharmaceutical value chain towards ensuring availability of medical products to the people that need them. An effective registration system ensures that the products that reach the end-users are quality assured, safe and efficacious.
c)	**Method of measurement:** This indicator is calculated by establishing if: 1) A country has a system for receiving applications, evaluating and providing marketing authorisation for medicines *2) Components of a registration system of medicines will be measured by existence of:* - *Legal mandate for registration of medicines/ marketing authorisation* - *NMRA use of national guidelines for registration of medicines* - *NMRA use of regional harmonized guidelines for registration of medicines* - *Year harmonized guidelines for registration of medicines came into force* - *Availability of procedures/SOPs for assessment* - *Existence of policy on abridged procedure for registration of medicines* - *NMRA use reference regulatory standard on abridged procedure for registration of medicines* - *Existence of a policy for waiver of registration requirement for certain categories of products* - *# of products given marketing authorization based on abridged procedure* - *Availability of assessors* - *Availability of updated drug register* - *NMRA communicates registrations of products to stakeholders* - *Existence of a mechanism for tracking registration application and timeline*

[12] A medicines registration system means a system that subjects all medical products to pre-marketing evaluation and issuing marketing authorization for ensuring that products conform to required standards of quality, safety, and efficacy.

	Existence of a policy for fast tracking registration of certain medicines
d)	**Evidence/ Sources**: WHO NRA GBT, CIRS OpERA programme, NMRA records, Government policies and legislation
e)	**Institutional Responsibility:** CIRS OpERA programme, NMRA
f)	**Measurement frequency:** Three yearly
g)	**Unit of measurement:** Yes/No
h)	**Data Type:** Qualitative
i)	**Indicator Classification:** Process
Indicator 8: Availability of Good Manufacturing Practice (GMP) inspection guidance and procedures13	
a)	**Purpose:** The indicator focuses on assessing the availability of core components of a GMP.
b)	**Rationale:** GMP is defined as a system for ensuring that products are consistently produced and controlled according to quality standards thereby minimizing the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product.[14] Good Manufacturing Practice (GMP) inspection is an important component of any registration system for ensuring delivery of a quality safe and efficacious medical product to patients and the end user. GMP inspection helps in avoiding unexpected contamination that may cause damage to health or even death. GMP inspection facilitates receipt of the right medication by patients which are correctly labelled and avoids ineffective treatment or adverse effects by avoiding insufficient or excess use of active ingredient. Ensuring GMP compliance by Africa-based manufacturers has both health and economic benefits of promoting access to quality products and expanding the pharmaceutical market through export promotion (Ref).
c)	**Method of measurement[15]:** This indicator is calculated by establishing: 1) Availability of GMP inspection guidance and procedure within the NMRA 2) This includes existence of core components of a GMP inspection system: - *Legal basis for Good Manufacturing Practice (GMP) inspections* - *Availability of harmonized guidelines for Good Manufacturing Practice (GMP) inspection* - *Good Manufacturing Practice (GMP) inspection assessment procedures/ SOPs* - *NMRA using harmonized guidelines for Good Manufacturing Practice (GMP) inspection* - *Year regional GMP guidelines came into force* - *NMRAs that participated in joint GMP inspection* - *Number of regional joint inspections participated in joint GMP inspection* - *Availability of policy on GMP assessment of pharmaceutical manufacturing sites using document review*

[13] **WHO NBT Sub Indicator CT01.04:** Legal provisions, regulations and/or guidelines requiring that Investigational Medical Products (IMPS) comply with Good Manufacturing Practice (GMP) for IMPS

[14] http://www.who.int/medicines/areas/quality_safety/quality_assurance/gmp/en/

[15] Users can use available indicators in the WHO GBT as proxy indicators

- *Reference regulatory standard used for GMP document review* - *Number of GMP inspection decisions made based on document review* - *Availability of GMP inspectors* - *NMRA conducting inspection of manufacturing sites (Local and international)*
d) Evidence/ Sources: WHO NRA GBT, NMRA records, Government policies and legislation, WHO Assessment Reports
e) Institutional Responsibility: NMRA
f) Unit of measurement: Yes/No
g) Measurement frequency: Annually
h) Data Type: Qualitative
i) Indicator Classification: Process
Indicator 9: Availability of a process to track product registration applications and timelines16
a) Purpose: The indicator assesses the availability of a process for tracking the status of an individual application from the time of submission of dossier to final decision by NMRA including both regulators and applicants' time. The process for tracking registration application and timelines includes electronic and/or manual system.
b) Rationale: The objective of this indicator is to assure whether timelines for the assessment of registration /marketing authorization applications exist, and whether the timelines are monitored by internal tracking systems to ensure compliance.
c) Method of measurement: This indicator is measured by: 1) Establishing if there was a process for tracking registration application and timelines include - Electronic - Manual system - Both electronic and manual systems
d) Evidence/ Sources: WHO NRA GBT, CIRS OpERA programme, NMRA records
e) Institutional Responsibility: NMRA
f) Measurement frequency: Annually
g) Unit of measurement: Yes/ No
h) Data Type: Quantitative

[16] WHO GBT Sub-Indicator: MA04.06: There are timelines for the assessment of the applications and an internal tracking system is established to follow the targeted time frames

i) **Indicator Classification:** Process

Indicator 10: Existence of a regional policy stimulating review timelines

a) **Rationale:** Delayed assessment and approval of applications for registration of medical products has a negative impact on access to these products by the people that need them. One of the major challenges that NMRAs face is frequent delays in processing applications for registrations of medical products which has most of the times led to backlogs. This indicator therefore measures existence of a regional policy stimulating review timelines and monitors the average timelines taken by NMRAs to register medical products with the view to inform actions for improving efficiency.

b) **Purpose:** The indicator is an average time taken by NMRAs to process an application from the time it is received to the time a decision. The indicator accounts for regulator's time only.

c) Method of measurement: This indicated is calculated as an average:

- Numerator: Total number of days taken by NMRA to decide on all applications reviewed each year
- Denominator: Total number of applications for which decisions were made in the year

Additional data is collected on average time on:

- The percentage of decisions on applications made within the regional stipulated timelines for
    - fast-tracked medicines and
    - normal review
- Number of Regional Joint Review
- Number of product applications received
- Total number of registration decisions made
- Number of Products:
    - Registered by the NMRA
    - Marketing authorization given using normal review
    - Marketing authorization given using fast-track review
    - Marketing authorization given using regional joint review
    - Marketing authorization given using based on abridged procedure
    - Marketing authorization given using joint GMP Inspections Reports
    - Marketing authorization given using document review

d) **Evidence/ Sources:** CIRS OpERA programme, NMRA records

e) **Institutional Responsibility:** NMRA

f) **Measurement frequency:** Annually

g) **Unit of Measurement:** Average

h) **Data Type:** Quantitative

i) **Indicator Classification:** Outcome
Indicator 11: Number of products applications with registration decisions17 per annum
a) Purpose: This indicator assesses the percentage of products applications from applicants whose registration decision has been made within the assessment time[18]
b) Rationale: One of the main challenges that National Medicines Regulatory Authorities in Africa are confronted with is lack of capacity to clear assessment of applications for registration of medical products within the expected timeframe. This leads to backlog[19] which hinder access to medical products needed within the national health system. Assessment of applications for product registration registered within assessment time will therefore enable the NMRAs to determine the level of backlog and come up with strategies for clearing it to facilitate access.
c) Method of measurement: The indicator is calculated as proportion of registration decisions made each year that are within the standard time[20]. - Numerator Total number of registration decisions made within standard time[21]X 100 - Denominator Total number of registration decisions Additional data is collected on: - Number of product applications received - Number of products given marketing authorization based on abridged procedure
d) Evidence/ Sources: CIRS OpERA programme, NMRA records
e) Institutional Responsibility: NMRA
f) Measurement frequency: Annually
g) Unit of Measurement: Percentage
h) Data Type: Quantitative
i) Indicator Classification: Outcome

[17] Registration decisions include both positive and negative decisions

[18] Assessment time refers to the timeline for registration of medical products agreed between the regulators and the industry and published in the guidelines for registration of medicines. The NMRAs and RECs will be required to include in their report the referred assessment time.

[19] Backlog is measures as the number products not assessed within the assessment time.

[20] Standard time refers to the timeline for registration of medical products agreed between the regulators and the industry and published in the guidelines for registration of medicines

[21] The review time is the time when the application is received and a decision is made but excluded the industry time for response to queries. For a manual system, consider sampling of applications

Indicator 12: Proportion of NMRAs participating in joint assessments
a) Purpose: This regional level indicator assesses the level of harmonisation in a region by measuring the proportion of NMRAs participating in regional joint assessments
b) **Rationale:** Joint regional assessments through RECs are aimed at facilitating quicker evaluation of applications thereby improving access to medical products by all the population in Africa. The joint assessment also builds capacities for NMRAs to enable them undertake quality and evidence-based decisions. Through joint regional activities, countries build confidence it each other facilitating eventual mutual recognition of regulatory decisions.
c) Method of measurement: - Numerator: Number of NMRAs participating in joint assessments in a particular year - Denominator: Number of NMRAs in the region
d) **Evidence/ Sources** REC records
e) **Institutional Responsibility:** NMRA
f) **Measurement frequency:** Annually
g) **Unit of Measurement:** Proportion
h) **Data Type:** Quantitative
i) **Indicator Classification: O**utput
Indicator 13: Proportion of product applications jointly assessed/ reviewed at regional level
a) Purpose: The indicator assesses of participation of NMRAs in joint regional activities and its impact on the national decision-making processes.
b) Rationale: Joint regional assessments implemented through RECs facilitate quicker evaluation of applications thereby improving access to medical products by African population. The joint assessment also builds capacities for NMRAs to enable them undertake quality and evidence-based decisions. Through joint regional activities, countries build confidence it each other facilitating eventual mutual recognition of regulatory decisions.
c) Method of measurement[22]: It is calculated as the proportion of regionally assessed[23] product registration applications whose registration decision is made within assessment time each year. - Numerator: Total Number of product applications with a decision stemming from Joint Review - Denominator: Number of jointly assessed applications at regional level.

[22] A mechanism to ensure country, regional and continental indicators will be developed

[23] Jointly assessed products include both regionally received applications and common applications received by more than one country in the region

Additional data is collected on: - Total Number of product applications with a decision - Total Number of product applications with a decision stemming from Joint Review - Proportion of product applications with a decision stemming from Joint Review - Number of jointly assessed applications at regional level - Average number of NMRA where jointly assessed applications resulted in decision for the NMRA.
d) **Evidence/ Sources:** CIRS OpERA programme, NMRA records
e) **Institutional Responsibility:** NMRA
f) **Measurement frequency**: Annually
g) **Unit of Measurement:** Ratio
h) **Data Type:** Quantitative
i) **Indicator Classification:** Outcome
Indicator 14: Proportion of NMRAs who made regulatory decisions within standard time24 based on regional reports/ assessment/s
a) Purpose: The indicator assesses reliance on regional assessments made at regional level. It measures the proportion of NMRAs who make decisions made at country level within the national registration timelines time based on regional report
b) Rationale: NMRAs who subsequently make regulatory decisions as a result of regional assessments facilitate quicker evaluation of applications thereby improving access to medical products by all the population in Africa. Through reliance on assessments made at regional level, countries build confidence it each other facilitating eventual mutual recognition of regulatory decisions and make quicker decisions on similar medical products.
c) Method of measurement: This indicator is calculated as a ratio: - Numerator: Number of NMRAs who made decisions based on regional reports/ assessment/s - Denominator: Total number of NMRAs in a region
d) Evidence/ Sources: CIRS OpERA programme, NMRA records
e) Institutional Responsibility: NMRA
f) Measurement frequency: Annually
g) Unit of Measurement: Proportion

[24] Assessment time is country specific

h) Data Type: Quantitative
i) Indicator Classification: Outcome
Indicator 15: Proportion of registrations made at country level based on regional report for which a decision was made within standard time
a) Purpose: The indicator assesses reliance on assessments made at regional level by measuring the proportion of applications whose decisions are made at country level within assessment time based on regional report
b) Rationale: NMRAs who subsequently make assessments as a result of regional assessments facilitate quicker evaluation of applications thereby improving access to medical products by all the population in Africa. Through reliance on assessments made at regional level, countries build confidence it each other facilitating eventual mutual recognition of regulatory decisions and make quicker decisions on similar medical products.
c) Method of measurement: - Numerator: Number of Medicines registered by NMRA annually using regionally agreed guidelines - Denominator: Number of applications made in line with regional procedures made in a country each year
d) Evidence/ Sources: CIRS OpERA programme, NMRA records
e) Institutional Responsibility: NMRA
f) Measurement frequency: Annually
g) Unit of Measurement: Proportion
h) Data Type: Quantitative
i) Indicator Classification: Outcome
Indicator 16: Proportion of NMRAs using regionally harmonised guidelines for product registration
a) Purpose: The indicator assesses the level of utilisation of regionally harmonised guidelines for registration of medicines by NMRAs in the region.
b) Rationale: Regionally agreed guidelines and procedures are being adopted by RECs to facilitate harmonised approaches, joint activities and work-sharing among NMRAs. The adoption and utilisation of regional guidelines is expected to have a positive impact on the technical capacities of NMRAs to regulate, and its efficiency, transparency and accountability in delivering on its mandate thereby facilitating access to medical products by the population.
c) Method of measurement: It is measured as percentage of NMRAs using regionally harmonised guidelines for 1) Registration of medicines - Numerator: Number of NMRAs utilising regionally agreed guidelines for registration of products

- Denominator Total number of NMRAs in the region
d) Unit of Measurement: Proportion
e) Measurement frequency: Annually
f) Evidence/ Sources: CIRS OpERA programme, NMRA records; REC records
g) Indicator Classification: Output
h) Data Type: Quantitative
i) Institutional Responsibility: NMRA, REC
Indicator 17: Proportion of NMRAs using regionally agreed systems and processes (assessment)
a) Purpose: The indicator, measured at the regional level, assesses the level of utilisation of regionally agreed systems and processes by NMRAs in the region.
b) Rationale: Regionally agreed systems and processes are being adopted by RECs to facilitate harmonised approaches, joint activities and work-sharing among NMRAs. The adoption and utilisation of regional systems and processes is expected to have a positive impact on the technical capacities of NMRAs to regulate, and its efficiency, transparency and accountability in delivering on its mandate thereby facilitating access to medical products by the population.
c) Method of measurement: - Numerator: Number of NMRAs utilising regionally agreed guidelines - Denominator: Total number of NMRAs in the region
d) Evidence/ Sources: NMRA records; REC records
e) Institutional Responsibility: NMRA, REC
f) Measurement frequency: Annually
g) Unit of Measurement: Proportion
h) Data Type: Quantitative
i) Indicator Classification: Output

Indicator 18: Joint Good Manufacturing Practices (GMP)25 inspections conducted regionally
a) Purpose: The indicator focuses on assessing the availability of core components of a GMP at regional and continental level as part of the harmonisation process
b) Rationale: NMRA participation in Joint GMP inspections is important for building capacity, work sharing and building confidence of the NMRA experts, and reduce the burden of inspections conducted by NMRAs in the same manufacturing sites. Through joint regional inspections, NMRA can clear their workload faster and generate the needed information that contributes to an efficient assessment process. Joint inspections implemented through RECs are one of the core components of the harmonisation process. GMP inspection is an important component of any registration system for ensuring delivery of a quality medial product to the end user by avoiding unexpected contamination that may cause damage to health or even death.
c) Method of measurement: This indicator will be measured by: - Number of manufacturing sites jointly inspected by the NMRA - Number of NMRAs that have participated in at least 1 joint GMP inspection each year.
d) Evidence/ Sources: REC records
e) Institutional Responsibility: NMRA, REC Secretariat
f) Measurement frequency: Annually
g) Unit of Measurement: Proportion
h) Data Type: Quantitative
i) Indicator Classification: Output

Indicator 19: Percentage of GMP inspection decisions made based on document review
a) Purpose: This indicator measures the level of reliance of the NMRA on other NMRAs and frameworks including to make decisions: - NMRAs within the region - NMRAs from other regions in Africa - NMRAs from outside Africa - PIC/S framework
b) Rationale: GMP documents review is a process whereby an NMRA relies on inspection reports of other competent NMRAs or PIC/S inspectors without conducting physical inspection of a manufacturing site. This procedure is key in facilitating consistency and uniformity of the GMP inspection processes and outcomes, and improved efficiency in regulatory decision making. It also reduces duplication of inspections conducted by multiple

[25] GMP is the part of quality assurance which ensures that products are consistently produced and controlled to the quality standard appropriate to their intended use and as required by the Marketing Authorization or product specification.

agencies thereby reducing the cost incurred by manufacturers.

c) Method of measurement:

The level of reliance is measured as a percentage of GMP inspections conducted through reliance on other NMRAs and frameworks calculated as:

- Numerator: Number of GMP inspection decisions made based on document review each year
- Denominator: Total number of GMP inspection decisions made by NMRA in the given year

d) Evidence/ Sources: NMRA records

e) Institutional Responsibility: NMRA

f) Measurement frequency: Annually

g) Unit of Measurement: Percentage

h) Data Type: Quantitative

i) Indicator Classification: Output

CATEGORY 5: FUNCTIONAL QUALITY MANAGEMENT SYSTEM (QMS)

Indicator 20: Implementation of Quality Management System (QMS) requirements by NMRA

a) Purpose: This indicator measures implementation of QMS by the NMRAs based on ISO 9001.

b) Rationale: The AMRH is promoting the implementation of QMS by the NMRAs based on ISO 9001. The overall objective of implementing QMS is to facilitate delivery of quality and consistent services to its customers. Attainment of a QMS in the NMRA, is an indication of Management commitment and willingness to improve the quality of its regulatory services

c) Method of measurement:

Attainment of QMS is measured by the extent of implementation of the various steps of QMS towards attainment of ISO 9001 Certification. The QMS steps which to be assessed include (yes/No):

- NMRA ISO 9001: 2015 QMS certified
- Existence of Quality Manual with clear quality policy and objectives; quality plan and indicators determined by availability of and procedures for documentation control
- A clear mapping, identification and documentation of regulatory processes based on functions e.g. registration of medicines and good manufacturing practice
- Designation of a Quality Manager with clear job description
- Training of staff on QMS
- Number of trained staff on QMS
- Availability of mechanism for periodic internal audits and follow-ups, investigation of non-compliance
- Implementation of corrective and preventive actions, procedure for dealing with complaints and record keeping.

- Implementation of Regional Economic Commissions (RECs) QMS in the NMRA based on ISO-9001:2015 standard
d) Evidence/ Sources: CIRS OpERA programme, NMRAs QMS Records
e) Institutional Responsibility: NMRA
f) Measurement frequency: Annually
g) Unit of measurement: Yes/ No
h) Data Type: Qualitative
i) Indicator Classification: Process
Indicator 21: Percentage of NMRAs ISO 9001: 2015 Certification
a) Rationale: ISO 9001 certification by the NMRA is evidence of high level of Management Commitment to persistently and consistently ensure efficient delivery of regulatory services in specific areas of regulatory function. This is an outcome of implementation of QMS with subsequent external audit and certification on specific regulatory processes and functions.
b) Purpose: The indicated assesses whether the NMRA consistently ensure efficient delivery of regulatory services in specific areas of regulatory function in accordance with ISO 9001 certification
c) Method of measurement: This is a regional indicator measured by evidence of ISO 9001 certification for both registration and GMP issued by an internationally recognised certification body upon audit of regulatory processes and subsequent fulfilment of the ISO requirements and standards by the NMRA. - Numerator: The number of NMRAs ISO Certified X 100 - Denominator: The total number of NMRAs assessed
d) Evidence/ Sources: NMRAs QMS Records
e) Institutional Responsibility: NMRAs
f) Measurement frequency: Annually
g) Unit of Measurement: Percentage
h) Data Type: Quantitative
i) Indicator Classification: Process

Indicator 22: Availability of mechanism for addressing customer concern26
a) Purpose: The indicator assesses the availability of mechanism for addressing customer concern
b) Rationale: Assessing the level of customer satisfaction with services offered by the NMRA provides an indication of the quality of services. Improving efficiency and effectiveness of service delivery that meet the needs and expectations of customers without compromising the quality, efficacy and safety of regulated products is at the core of regulatory excellence. Various approaches are employed by NMRAs to provide services that meet customer needs including mechanisms for customer complaint procedure; Client Service Charter that serve as an agreement between the NMRA and its customers; and customer satisfaction surveys.
c) Method of measurement: This indicator will be measured by assessing availability of mechanisms for customer complaint procedure; Client Service Charter; and customer satisfaction surveys.
d) Evidence/ Sources: WHO NRA Global Benchmarking Tool, NMRAs, Customer Complaint Reports, Customer Satisfaction Surveys/Index
e) Institutional Responsibility: NMRAs
f) Measurement frequency: Annually
g) Unit of Measurement: Yes/ No
h) Data Type: Qualitative
i) Indicator Classification: Process
CATEGORY 6: INFORMATION MANAGEMENT SYSTEM (IMS)
Indicator 23: Implementation of requirements for an integrated IMS
a) **Rationale:** A robust AMRH information management system (IMS) is key for supporting the technical aspects of medicines regulation. Implementation of IMS by NMRA facilitates efficiency and effectiveness of business processes, improves transparency; facilitates decision making process, sharing and exchange of information among NMRAs and stakeholders; and timeliness of approval of registration decisions. A functional IMS for NMRA is determined by well-defined dossier management and internal business processes (workflow management) supported by key modules including; product registration; GMP; premises registration; inspections; imports and exports; and finance modules. A common integrated information management system for drug registration of medical products among NMRAs participating in a regional medicines regulatory harmonization scheme is key to ensure successful implementation of harmonized guidelines. Attainment of an integrated IMS is determined by the level of implementation of all the steps in the critical development phase.
b) **Purpose:** The indicator assess whether the NMRA has attained requirements for an integrated Information Management System (IMS) which is able to facilitate efficiency and effectiveness of business processes, improves transparency; facilitate decision making process, sharing and exchange of information among NMRAs and stakeholders; and timeliness of approval of registration decisions
c) Method of measurement: This indicator is measured by whether the NMMRA has a functional IMS. In addition, the level of NMRA implementation of the following AMRH IMS modules is also measured: **1) Implementation of IMS modules by NMRA**

[26] WHO GBT Sub-Indicator RS05.10: A mechanism to evaluate the satisfaction of internal and external customers and other interested parties is in place for system improvement

- Product module
- GMP module
- Premises module
- Inspection module
- Import and export module
- Finance management module

2) Integrated IMS at regional level

- Availability of NMRA Website (refer to indicator 29.2)
- NMRA sharing regulatory information with others in the REC region

d) **Evidence/ Sources:** WHO NRA Global Benchmarking Tool, NMRAs; IMS

e) **Institutional Responsibility:** NMRAs

f) **Measurement frequency:** Annually

g) **Unit of measurement:** Yes/ No

h) **Data Type:** Quantitative

i) **Indicator Classification:** Output

CATEGORY 7: LEVEL OF TRANSPARENCY

Indicator 24: Availability of key regulatory information to the general public using different platforms

a) Purpose: The indicator assesses availability of regulatory information to the public domain and sharing of information at the regional, continental and international level is key for public confidence and NMRA credibility.

b) Rationale: Availability of regulatory information to the public domain and sharing of information at the regional, continental and international level is key for public confidence and NMRA credibility. The AU Model law advocates for creation of an information management system which allows for sharing information at regional and continental levels in accordance with national laws, bilateral and multilateral agreements.

c) Method of measurement: This indicator is measured by determining the existence of legal basis for transparency and availability of key regulatory information to the public using different platforms[27]. Information to be made publicly available include;

- Medicines Policy
- Medicines Law
- Regulations
- Guidelines
- Procedures for applications and decision-making processes
- Summary inspection reports
- List of registered premises, registered products, renewals and withdrawals

[27] Platforms for information sharing include government gazette, website, scheduled meetings, workshops and/or awareness seminars

- Appeals against NMRA decision
- Safety alerts
- Banned products
- Withdrawn products
- Recalled products
- Prohibited products
- Restricted products

d) Evidence/ Sources: NMRAs Website, Government Gazette and WHO reports

e) Unit of measurement: Yes/ No

f) Measurement frequency: Annually

g) Indicator Classification: Output

h) Data Type: Qualitative

i) Institutional Responsibility: NMRAs

Indicator 25: Engagement of stakeholders on different platform(s)

a) Purpose: This indicator assess availability of NMRA stakeholders' engagement platform(s) aimed at ensuring transparency and accountability of the NMRA to all stakeholders

b) Rationale: Consultation and involvement of stakeholders in the formulation of regulatory policies, regulations and guidelines is key for transparency, accountability and stakeholder's buy-in. Stakeholder engagement is important for discussing matters of common interest and agree on implementation modalities. Stakeholders may include parliamentarians, policy makers, scientists, academia, industry, and civil society, representatives of health professional, consumers and patients.

c) Method of measurement: The indicator measures the level of transparency and accountability of the NMRA. Stakeholders' engagement will be assessed by the number of platforms the NMRA has used to engage stakeholders during the reporting period including:

- Scheduled meetings, workshops and/or awareness seminars between the NMRA and a specific target audience
- Open days to the public for information, education and awareness of regulatory decisions and impact to public health
- Existence of mechanisms for making guidelines that are legally binding
- The level of stakeholder engagement
- Mechanisms for stakeholder engagement
- Existence of National Association(s) of Pharmaceutical Industries

d) Evidence/ Sources: NMRA Records, REC Records, NEPAD Agency records

e) Institutional Responsibility: NMRAs

f) Measurement frequency: Annually

g) Unit of Measurement: Number
h) Data Type: Quantitative
i) Indicator Classification: Process
CATEGORY 8: NMRA HUMAN RESOURCES CAPACITY
Indicator 26: Medical products regulatory experts' density
a) Rationale: Availability of the requisite number of staff with relevant qualifications[28], skills and knowledge to perform core regulatory and managerial functions is a critical factor for NMRA performance. Relevant qualifications, skills and knowledge for regulatory experts is as defined in the AU-AMRH Regulatory Competence Framework. Different expertise is required to perform different regulatory functions related to registration of medical products such as product evaluation and registration, inspection of manufacturing sites.
b) Purpose: This indicator assesses the requisite number of staff with relevant qualifications, skills and knowledge to perform core regulatory and managerial functions is a critical factor for NMRA performance
c) Method of measurement: The indicator measured by: 1) The number of product evaluation and registration experts as a proportion of applications received per year - **Numerator:** The total number of applications received in 12 months - **Denominator:** The total number of product evaluation and registration experts with relevant qualification and skills OR 2) The number of GMP inspectors per GMP inspections conducted in a year - **Numerator:** The total number of planned GMP inspections in 12 months - **Denominator:** The total number of GMP Inspectors with relevant qualification and skills
d) Unit of Measurement: Ratio
e) Measurement frequency: Annually
f) Evidence/ Sources: CIRS OpERA programme, NMRAs records
g) Indicator Classification: Input
h) Data Type: Quantitative
i) Institutional Responsibility: NMRAs
Indicator 27: Internal NMRA capacity
a) Purpose: This indicator measures the percentage of external expertise used by the NMRA per regulatory function.
b) Rationale: Availability of internal NMRA regulatory expertise is key for self-reliance and sustainability. However, there is need to utilise external expertise for certain specialised tasks required by the NMRA. It is thus fundamental for the NMRA to ensure a balance between utilisation of internal and external expertise.
c) Method of measurement: Internal NMRA capacity is calculated as follows: - Numerator: Number of external expertise per regulatory function[29] x 100

[28] Relevant qualifications is clearly defined/itemised in the data collection tool
[29] Indicator measures registration experts (Assessors) and GMP inspectors

-	Denominator: Total number of NMRA expertise undertaking the function
d)	**Evidence/ Sources** NMRAs
e)	**Institutional Responsibility:** CIRS OpERA programme, NMRA records
f)	**Unit of Measurement:** Percentage
g)	**Measurement frequency:** Annually
h)	**Data Type:** Quantitative
i)	**Indicator Classification:** Input
CATEGORY 9: PARTNERSHIPS AND COORDINATION	
Indicator 28: Partnership coordination towards collective impact on regulatory systems strengthening	
a)	**Purpose:** This indicator assesses the number of partnerships that that are coordinated by AMRH programme towards collective impact on regulatory systems strengthening.
b)	**Rationale:** There are various partners30 providing support to NMRAs due to regulatory complexities and extent of scientific expertise required for regulatory systems strengthening in Africa. To attain a collective impact, it is crucial for the NMRAs to have mechanisms to coordinate partners to avoid any duplication of efforts and waste limited resources. It is also relevant to identify the type of support provided by these partners so as to align them to the MRH vision and have a unified approach as per the established AU frameworks (AMRH, Pharmaceutical Manufacturing Plan for Africa (PMPA) and the AU Roadmap for Shared Responsibility and Global solidarity for the AIDS, TB and malaria response in Africa. etc.) This indicator will identify and document best practices in partner coordination for collective impact at the national, regional and continental level. Given that NMRAs are expected to cooperate with other national, regional and continental medical products regulatory agencies and share pharmaceutical intelligence on products that pose public health risks, it is imperative for the agency to take appropriate measures to ensure effective bilateral, regional and international co-operation. This will contribute to combatting the production, circulation and use of SSFFC medical products, illicit drugs, narcotics and psychotropic substances.
c)	**Method of measurement:** The indicator will be measured by: - Number of partners providing support to NMRA on various regulatory functions/mechanisms at country level - Type of support provided - Availability of mechanism for coordination of partners at country level
d)	**Evidence/ Sources:** Mutual recognition agreements, MOUs, Requests sent to/received from partners, National partnership agreements
e)	**Institutional Responsibility:** NMRA, Ministry of Health, RECs and NEPAD Agency
f)	**Measurement frequency: Annually**
g)	**Unit of measurement: Agreements; MOUs**
h)	**Data Type: Qualitative**
i)	**Indicator Classification: Input**
Indicator 29: Proportion of partners that are aligning to the AMRH framework	
a)	**Purpose:** This indicator will measure the proportion of partners supporting regulatory systems strengthening in an NMRA that align to the AMRH framework
b)	**Rationale:** Partnerships are important in facilitating knowledge transfer as well as provision of additional resources for regulatory systems

[30] Partners include national, regional or continental organisations providing financial, technical and any other in-kind support towards strengthening different regulatory functions.

	strengthening. Development partners and international agencies provide support to NMRA on various regulatory functions/mechanisms at country level. Considering the need for efficient utilisation of resources, partners' alignment to the regulatory systems strengthening agenda and harmonisation promoted through the AMRH is imperative for complementarity and minimising duplication.
c)	**Method of measurement:** Partners will include those providing financial, technical and any other in-kind support towards strengthening different regulatory functions. - Numerator: Number of partners aligning to the AMRH framework - Denominator: Total number of partners supporting the NMRA
d)	**Evidence/ Sources:** Income statement of the NMRA, MOUs, Mutual recognition agreements
e)	**Institutional Responsibility:** NMRA and Ministry of Health
f)	**Measurement frequency:** Annually
g)	**Unit of measurement: ratio**
h)	**Data Type:** Quantitative
i)	**Indicator Classification:** Input

ANNEX 7.4: ETHICS CLEARANCE CERTIFICATES

R14/49 Mrs Margareth Ndomondo-Sigonda

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150751

NAME: (Principal Investigator)	Mrs Margareth Ndomondo-Sigonda
DEPARTMENT:	Phamarcy and Pharmacology East African Community Secretariat Health Department, Ministries of Health Departments of Pharmaceutical Services National Medicine Authorities
PROJECT TITLE:	Evaluation of Medicines Regulatory Interventions in the East African Community Region
DATE CONSIDERED:	31/07/2015
DECISION: CONDITIONS:	Approved unconditionally
SUPERVISOR:	Prof Shan Naidoo
APPROVED BY:	Professor P. Cleaton-Jones,Chairperson, HREC (Medical)
DATE OF APPROVAL:	08/04/2016

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated,from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review in July and will therefore be due in the month of July each year.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

EAST AFRICAN COMMUNITY
SECRETARIAT

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Date : 2nd Feb, 2016

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DISPATCHED
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Dear Permanent/Principal Secretary,

RE: REQUEST FOR SUPPORT TO CONDUCT INTERVIEWS AND DATA COLLECTION BY A PhD STUDENT ON EAST AFRICAN COMMUNITY MEDICINES REGULATORY HARMONIZATION PROJECT FROM MARCH TO JUNE, 2016

The East African Community Secretariat is currently coordinating the implementation of the East African Medicines Regulatory Harmonization (EAC-MRH) Programme, which aims to improve access to priority medicines through harmonization of medicines regulation, requirements, processes and standards. The programme was launched in March, 2012; Phase I of the Programme ended in December, 2014 with approval of EAC harmonized technical guidelines and requirements for regulation of medicines by the 29th Ordinary Meeting of the EAC Council of Ministers ***(EAC/CM 29/Decision 36)*** and is currently implementing Phase II of the programme.

The implementation of the programme in the EAC region has attracted attention of medicines regulatory sector, scholars, academicians and policy makers. It is in this regard that one of the Doctor's of Philosophy student from the University of Witwatersrand has submitted her compliment to the East African Community Secretariat requesting for introduction of her to the Partner States, to conduct interviews and data collection in line with the current implementation of EAC -MRH Programme.

The purpose of this letter therefore, is to introduce Ms. Margareth Ndomondo Singonda a PhD student at the University of Witwatersrand South Africa. Ms. Ndomondo will be travelling across the East African Community Partner States collecting data and conducting interviews on East African Community Medicines Regulatory Harmonization Programme.

The EAC Secretariat is kindly requesting the Partner States responsible institutions (National Medicines Regulatory Authorities) and individuals to accord her the necessary support and assistance.

It is expected that the findings from her PhD study will guide and improve future undertakings of similar nature, in the EAC and other RECs intending to implement the same programme.

Attached herewith, please find a concept note/ study protocol describing the approach and methodology and respondents who will be contacted.

Please accept, Permanent/Principal Secretary, the assurances of our highest consideration.

Hon. Jesca Eriyo,
Deputy Secretary General
(Productive and Social Sectors)

For: **SECRETARY GENERAL**

2

THE UNITED REPUBLIC OF TANZANIA

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NIMR/HQ/R.8a/Vol. IX/2184

02nd May 2016

Margaret Ndomondo Sigonda
Department of Pharmacy and Pharmacology
Faculty of Sciences, University of Witwatersrand
South Africa

CLEARANCE CERTIFICATE FOR CONDUCTING MEDICAL RESEARCH IN TANZANIA

This is to certify that the research entitled: Evaluation of Medicines Regulatory Interventions in the East Africa Community Region, (Ndomondo-Sigonda M *et al*), has been granted ethical clearance to be conducted in Tanzania.

The Principal Investigator of the study must ensure that the following conditions are fulfilled:

1. Progress report is submitted to the Ministry of Health, Community Development, Gender, Elderly & Children and the National Institute for Medical Research, Regional and District Medical Officers after every six months.
2. Permission to publish the results is obtained from National Institute for Medical Research.
3. Copies of final publications are made available to the Ministry of Health, Community Development, Gender, Elderly & Children and the National Institute for Medical Research.
4. Any researcher, who contravenes or fails to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine. NIMR Act No. 23 of 1979, PART III Section 10(2).
5. Site: Tanzania
   Approval is for one year: 02nd May 2016 to 01st May 2017.

Name: Dr Mwelecele N Malecela

Signature
CHAIRPERSON
MEDICAL RESEARCH
COORDINATING COMMITTEE

Name: Prof. Muhammad Bakari Kambi

Signature
CHIEF MEDICAL OFFICER
MINISTRY OF HEALTH, COMMUNITY
DEVELOPMENT, GENDER, ELDERLY
&CHILDREN

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DED
DMO

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KEMRI/RES/7/3/1 **May 10, 2016**

TO: **MARGARET NDOMONDO-SIGONDA, (PRINCIPAL INVESTIGATOR)**
UNIVERSITY OF WITWATERSRAND,
JOHANNESBURG, SOUTH AFRICA

Dear Madam,

RE: **NON-KEMRI PROTOCOL NO. 523 (*RESUBMISSION OF INITIAL SUBMISSION*): EVALUATION OF MEDICINES REGULATORY INTERVENTIONS IN THE EAST AFRICAN COMMUNITY REGION**

Reference is made to your letter dated 4th April, 2016. KEMRI/Scientific and Ethics Review Unit (SERU) acknowledges receipt of the revised study protocol on April 06, 2016.

This is to inform you that the Committee notes that the issues raised at the 249th meeting of the KEMRI/Ethics Review Committee (ERC) held on March 15, 2016 have been adequately addressed. Consequently, the study is granted approval for implementation effective this day **10th May, 2016** for a period of one year. Please note that authorization to conduct this study will automatically expire on **May 09, 2017.** If you plan to continue data collection or analysis beyond this date, please submit an application for continuation approval to SERU by **March 28, 2017**.

You are required to submit any proposed changes to this study to SERU for review and the changes should not be initiated until written approval from SERU is received. Please note that any unanticipated problems resulting from the implementation of this study should be brought to the attention of SERU and you should advise SERU when the study is completed or discontinued.

You may embark on the study.

Yours faithfully,

FOR:

DR. EVANS AMUKOYE,
ACTING HEAD,
KEMRI/SCIENTIFIC AND ETHICS REVIEW UNIT

Republic of Burundi

Bujumbura 1st March 2016

Ministry of Public Health and AIDS Control
Permanent Secretary
Tél : +257 22 24 25 42

Margareth Ndomondo-Sigonda
Faculty of Health Sciences
Department of Pharmacy and Pharmacology
7 York road, Park town 2193,
South Africa

Dear Madam,

Re: Your request for permission to conduct Research in the Republic of Burundi on "Evaluation of Medicines Regulatory interventions in the East African Community Region"

The Ministry of Public Health and AIDS Control of Burundi has, in its National Health Policy as well as in the National Health Development Plan, identified as priority (among others) the regulation of Medicine Sector. At the same time, the East African Community, trough Partner States' Ministry of Health, is implementing harmonized regulatory tools and standards with a focus on harmonization of medicines registration systems.

Your study is welcome as it will help in evaluating the current regulatory harmonization actions, identifying the bottle necks, finding solutions and helping decision makers.

The purpose of this letter, therefore, is the give you the permission to conduct Research in the Republic of Burundi on "Evaluation of Medicines Regulatory interventions in the East African Community Region".

Accept, Dear Madam, the expression of my highest considerations.

Mr. Elam SENKOMO
Permanent Secretary

Copy:
- Dr Josiane NIJIMBERE
  Minister of Public Health and AIDS Control
- Mr. Emmanuel BAMENYEKANYE
  Head of the Department of Pharmacy, Medicine and Laboratory

REPUBLIC OF RWANDA

Kigali, on 01 DEC 2015

No20/ 5545 /DGCPHS/PH/ 2015

MINISTRY OF HEALTH
P.O BOX 84 KIGALI - RWANDA
www.moh.gov.rw

Margareth Ndomondo-Sigonda

E-mail: 766425@students.wits.ac.za

Re: Request for permission to conduct a Research

Dear Madam,

Reference is made to your request dated on 15/09/2015 requesting for permission to conduct a research entitled "***Evaluation of Medicine Regulatory interventions in East Africa Community Region***",

I am pleased to inform you that the Ministry of Health has no objection on your request. However, we recommend that if the scope can allow the incorporation of other interviewees like the heads of vaccines and biosimilars for better decision making.

We wish you all the best.

MINISTERE DE LA SANTE

Dr. Agnes BINAGWAHO
Minister of Health

Cc:

- Honorable Minister of State in charge of Public health and Primary Health care
- Permanent Secretary/Ministry of Health
- Chair of National Health Research Committee
  Kigali

REVOLUTIONARY GOVERMENT OF ZANZIBAR
MINISTRY OF HEALTH

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Ref. No. BD 301/366/01

30th September, 2015.

MARGARETH NDOMONDO - SIGONDA,
JOHANNESBURG,
SOUTH AFRICA.

REF: REQUEST FOR PERMISSION TO CONDUCT RESEARCH IN THE UNITED REUBLIC OF TANZANIA(ZANZIBAR) ON EVALUATION OF MEDICINES REGULATORY INTERVENTIONS IN THE EAST AFRICAN COMMUNITY REGION

Kindly refer to the heading above.

We are pleased to receive your letter requesting a permission to carry out an interview with the Chief Pharmacist in the Ministry of Health and Registrar at Zanzibar Food and Drugs Board, as your need to conduct research entitled 'Evaluation of Regulatory Interventions in the East African Community (***EAC***) Region.

As a Ministry of Health, Zanzibar, we are enthusiastic about the opportunity to meet and assist you on this subject matter.

We look forward meeting you soon.

Thank you for the continued cooperation.

MINISTRY OF HEALTH

S. Jiddawi

DR. MOHAMMED S. JIDDAWI - MD,
PRINCIPAL SECRETARY,
MINISTRY OF HEALTH,
ZANZIBAR.