An Evaluation of the Regulatory Review Systems in the East African Community: Contributing to the Establishment of the African Medicines Agency

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“I can do all this through him who gives me strength.”
Philippians 4:13

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ABSTRACT

The African Medicines Agency (AMA) has been established as the main driver for "enhancing the regulatory oversight of medicines and vaccines across the African continent". A successful AMA will need strong and agile NRAs and REC-MRH programmes/ authorities to address most of the regulatory challenges. It is therefore critical to evaluate the regulatory review systems and performance of the regional medicines harmonisation progress to determine their capacity to fully support the AMA. The aim of this research programme was to evaluate the regulatory review systems in the East Africa Community as it contributes to the establishment of the African Medicines Agency.

This started with an overview of the EAC medicines regulatory landscape where the history, objectives, scope, organisational structure, successes and benefits of the EAC-MRH was obtained from existing literature. This was followed by an assessment of the review systems of the seven NRAs in the EAC region, using an established standardised questionnaire, (Optimising the Efficiency of Regulatory Agencies), which captures review processes was completed by the Head of the medicine's registration division in each of the seven NRAs. A country report based on the completed questionnaire for each NRA was validated by the heads of the respective agencies. The Process Effectiveness and Efficiency Rating (PEER) questionnaire was then used to evaluate the effectiveness and efficiency of the current East African Community Medicines Regulatory Harmonization (EAC-MRH) operating model, and was completed by seven EAC assessors and 14 pharmaceutical companies coupled with Semi-structured interviews Lastly, using existing literature, a comparison of the outcome of this study on the EAC-MRH was conducted with the Southern African Community Regional Initiative (ZaZiBoNa) and the West African Community (WAC)-MRH initiative to learn best practices and share experience.

The results of this study on the evaluation of the effectiveness and efficiency of the EAC regional initiative, indicated that the approach has been of considerable value since its inception in 2012 as it moves towards achieving its main objectives of approval of medicines, information sharing among regulators and capacity building for assessments, resulting in quicker access and increased availability of medicines for patients in the region. Pharmaceutical companies outlined how the initiative has facilitated the harmonisation of registration requirements across the EAC region leading to one registration for all countries and a reduction of the workload for both applicants and assessors. In addition, it is expected that shorter timelines for approval will lead to improved access to quality-assured essential medicines in the region. However, the key challenges identified by the agencies in the Region which have hindered the expected effectiveness and efficiency of this initiative were the lack of a centralised submission and tracking system; a lack of mandated registration; inadequate human

resources, manufacturers' failure to submit the exact same dossier to all countries of interest; a lack of an integrated information management system; a lack of information on national medicines regulatory authority or EAC websites; and challenges in monitoring and tracking assessment reports. A key strategy proposed by both agencies and applicants was the establishment of a regional administrative body to centrally receive and track EAC applications and the eventual establishment of a Regional EAC Medicines Authority.

Good Review Practices of agencies in the East African Medicine Regulatory Harmonisation Initiative could still be improved. This study has demonstrated how the EAC-MRH performs regulatory reviews in order to improve the capacity of NRAs. For the AMA to be successful, country regulatory processes need to be streamlined and differences in country requirements minimised. The use of a robust information technology system for the central tracking of EAC products is essential to address the identified challenges and improve regulatory effectiveness and efficiency. To expedite the process and to ensure transparency, information on decision making should be available on national and regional websites. Strategies for enhancement include improving the capacity of assessors, work and information sharing and a coordination mechanism for the regional joint assessment, with the eventual establishment of a regional medicine agency. As this is the first study evaluating the performance of the EAC work sharing initiative, it was believed that the system performs efficiently. However, in some member countries an EAC positive recommendation does not directly result in an individual country approval. While harmonisation is key to ensuring access to safe, effective, and high-quality medicines, accessibility and affordability also need to be addressed to realise the full benefits of the medicines regulatory harmonisation initiative. Full implementation of the centralised procedure is critical to address such issues.

The recommendations from this study included measuring and monitoring timelines, the availability of submission guidelines, the training and capacity building of regulatory reviewers as well as the publication of decision-making outcomes and the implementation of a central submission and tracking system. If these recommendations are implemented, it should improve the effectiveness and efficiency of this regional initiative and thus support the African Medicines Agency .

PUBLICATIONS AND PRESENTATIONS

Journal Articles

Chapter 1: Ngum, N., Ndomondo-Sigonda, M., Walker, S. and Salek, S., 2023. Regional regulatory harmonisation initiatives: Their potential contribution to the newly established African Medicines Agency. Regulatory Toxicology and Pharmacology 145 (2023) 105497. (Appendix 1)

Chapter 3: Ngum, N., Ndomondo-Sigonda, M., Walker, S. and Salek, S., 2024. Assessment and comparison of Good Review Practices of the seven agencies in the EAC region using a validated OpERA Questionnaire. A manuscript entitled "Evaluation of the good review practices of countries participating in the EAC joint assessment" (Appendix 1- *Submitted*)

Chapter 4: Ngum, N., Ndomondo-Sigonda, M., Walker, S. and Salek, S., 2024. Evaluation of the Review Models and Approval Timelines of Agencies participating in the East African Medicine Regulatory Harmonisation Initiative: Alignment and Strategies for moving Forward has been drafted and will be submitted to Frontiers in Medicine. (Appendix 1-*Submitted*)

McAuslane N, Bujar M, Sithole T, Ngum N, Owusu-Asante M, Walker S. (2023). 'Evaluation of Risk-Based Approaches to the Registration of Medicines: Current Status Among African Regulatory Authorities.', Pharmaceutical Medicine, https://doi.org/10.1007/s40290-023-00472-0

Chapter 5: Ngum, N., Mashingia, J., Ndomondo-Sigonda, M., Walker, S. and Salek, S., 2022a. Evaluation of the effectiveness and efficiency of the East African Community joint assessment procedure by member countries: The way forward. Frontiers in Pharmacology, 13. https://doi:10.3389/fphar.2022.891506. (Appendix 1)

Mashingia J., Ngum N., Ndomondo-Sigonda M., Kermad A., Bujar M., Salek S., Walker S., (2023) Regulatory performance of the East African Community joint assessment procedure: The way forward for regulatory systems strengthening. Regulatory Toxicology and Pharmacology. 140 (2023) 105383 (Appendix 1)

Chapter 6: Ngum, N., Mashingia, J., Ndomondo-Sigonda, M., Walker, S. and Salek, S., 2022b. Evaluation of the effectiveness and efficiency of the East African community joint

assessment procedure by pharmaceutical companies: Opportunities for improvement. Frontiers in Pharmacology.

Chapter 7: Tariro Sithole, Nancy Ngum, Mercy Owusu-Asante, Sam Salek, Stuart Walker. 2024. Comparison of Three Regional Medicines Regulatory Harmonisation Initiatives in Africa: Opportunities for Improvement and Alignment the International Journal of Health Policy and Management. doi10.34172/ijhpm.2024.8070 (Appendix 1. *In Press)*

Chapter 8: Ngum N., Chamdimba C., Mbonyingingo D., Siyoi F., Bienvenu E., Arik M., Fimbo A., Nahamya D., Simai B., Salek S., Walker S. 2024. A proposed new improved Review Model for the EAC-MRH Initiative. Submitted in Regulatory Toxicology and Pharmacology

Poster Presentations

Ngum, N., Salek, S. and Walker, S. (2023). Evaluation of the Effectiveness and Efficiency of Ten Years' Experience with the East Africa Community Joint Assessment". Drug Information Association (DIA) Global Annual Meeting 2023, 25-29 June 2023, Boston, United States of America. (Appendix 2).

Ngum, N., Salek, S. and Walker, S. (2023). Evaluation of the Effectiveness and Efficiency of seven years' experience with the East African Community Joint Assessment. 6th Biennial Scientific Conference on Medical Products Regulation in Africa (SCoMRA VI), 5-7 December, Cairo, Egypt.

Ngum, N., Salek, S. and Walker, S. (2024). Evaluation of Good Review Practices in Member Agencies of the East African Medicines Regulatory Harmonisation Initiative. Annual LMS Research Conference 2024, 11 June 2024, University of Hertfordshire, United Kingdom. (Appendix 2-).

Ngum, N., Salek, S. and Walker, S. (2024). Evaluation of Good Review Practices in Member Agencies of the East African Medicines Regulatory Harmonisation Initiative. Drug Information Association (DIA) Global Annual Meeting 2024, 16-20 June 2024, San Diego, United States of America. (Appendix 2-).

Oral Presentations

Ngum, N., Salek, S. and Walker, S. (2021). Evaluation of the EAC joint assessment: Challenges and opportunities for the way forward. Oral presentation at OpERA Regional Forum Africa/Asia/Middle East Workshop convened by Centre for Innovation in Regulatory Science (CIRS), 20 December 2021, Virtual.

Ngum, N., Salek, S. and Walker, S. (2022). Evaluation of the EAC joint assessment: Challenges and opportunities for the way forward. Oral presentation at The Second CIRS African Regulatory Advisory Committee Workshop convened by Centre for Innovation in Regulatory Science (CIRS), 17 February 2022, Virtual.

Ngum, N., Salek, S. and Walker, S. (2022). Utilising metrics to measure and improve performance of EAC-MRH Regional Initiative. Oral presentation at Centre for Innovation in Regulatory Science webinar on Collaborative models: How do these fit into the regulatory agency toolkit. 05-06 July 2022. Virtual.

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Ngum, N., Salek, S. and Walker, S. (2023). Practical experience: Implementing collaborative regional models. What are the key opportunities for harmonization, improved quality and patient access and the importance of metrics to support. Oral presentation at Centre for Innovation in Regulatory Science Workshop and Annual Regulators Forum held at Voco Orchard Singapore, 581 Orchard Road, Singapore: 27 April 2023.

Ngum, N., Sithole T., Owusu-Asante, M., Salek, S. and Walker, S. (2023). Work-sharing and joint assessments: Changing mindsets through collaborations and process tools. Oral presentation at FRPath Webinar titled “Considerations for optimizing the use of reliance-based regulatory pathways” on 18 May 2023.

Ngum, N., Sithole T., Owusu-Asante, M., Salek, S. and Walker, S. (2023). Assessment of Performance of Regional MRH Programmes. Oral presentation at The Eighth African Medicines Regulators Conference (AMRC), Kigali Rwanda 23-24 August 2023.

Ngum, N. (2023). Availability and Accessibility of Medicines in Africa. Oral presentation at African Pharmaceutical Distribution Association Thematic Meeting 9-10 October 2023, Kigali Rwanda.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

AfCFTA	African Continent Free Trade Area
ABREMA	South Sudan; Burundi Food and Medicines Regulatory Authority
ABRF	African Blood Regulators Forum
AMA	African Medicines Agency
AMDF	African Medical Devices Forum
AMQF	African Medicines Quality Forum
AMRH	African Medicines Regulatory Harmonisation
AU	African Union
AUC	African Union Commission
AUDA-NEPAD	African Union Development Agency
AVAREF	African Vaccines Regulatory Forum
BCG	Boston Consulting Group
CHMP	Committee for Medicinal Products for Human use
CIRS	Centre for Innovation in Regulatory Science
COVID-19	Corona Virus Disease
CRO	Contract Research Organization
CTD	Common Technical Document
DFCA	Drug and Food Control Authority
DRC	Democratic Republic of Congo
EAC	East African Community
EAC-MRH	East African Community Medicines Regulatory Harmonisation
ECOWAS	Economic Community of West Africa States
ECCAS	Economic Community of Central African States
ECCAS-MRH	Economic Community of Central African States Medicines Regulatory Harmonisation
EMA	European Medicines Agency
EMP	Evaluation of Medicinal Products
EU	European Union

EWG	Expert Working Groups
FDA	Food And Drugs Association
FGD	Focus Group Discussions
GBT	Global Benchmarking Tool
GMP	Good Manufacturing Practices
GReVP	Good Review Practices
HIV & AIDS	Human Immunodeficiency virus & Acquired Immune Deficiency Syndrome
ICH	International Council for Harmonization of Technical Requirements of Pharmaceuticals for Human Use
IGAD	The Intergovernmental Authority on Development
IGAD-MRH	The Intergovernmental Authority on Development Medicines Regulatory Harmonisation
IMS	Information Management System
ISO	International Organisation for Standards
IT	Information Technology
IVD	In Vitro Diagnostics
JA	Joint Assessment
KPPB	Kenya Pharmacy and Poisons Board
MA	Marketing Authorisation
MCAZ	Medicines Control Authority of Zimbabwe
MER	Medicines Evaluation and Registration
ML	Maturity Level
MPRR	Medicines Policy and Regulatory Reforms
MRH	Medicines Regulatory Harmonisation
NAS'S	New Active Substance's
NCE	New Chemical Entities
NDA	National Drug Authority
NMRA	National Medicines Regulatory Authorities
NRA	National Regulatory Agency
OCEAC	Organization of Coordination for the Fight Against Endemic Diseases in Central Africa

OPERA	Optimising Efficiencies in Regulatory Agencies
PEER	Process Effectiveness and Efficiency Rating
PEER-IND	Process Effectiveness and Efficiency Rating for Industry
PIC/S	Pharmaceutical Inspection Cooperation Scheme
PLOS	Public Library of Science
PPB	Pharmacy and Poisons Board
PQ	Pre-qualification
PV	Pharmacovigilance
RCOREs	Regional Centers of Regulatory Excellence
RCD	Regulatory Capacity Development
REC	Regional Economic Communities
REC-MRH	Regional Economic Communities Medicines Regulatory Harmonisation
RFDA	Rwanda Food and Drugs Authority.
RIMS	Regulatory Information Management Systems
RTO	Regional Technical Officers
SADC	Southern African Development Community
SADC-MRH	Southern African Development Community Medicines Regulatory Harmonisation
SAHPRA	South African Health Products Regulatory Authority
SCOPUS	Indexing Database
SF	Substandard and Falsified
SOPs	Standard Operating Procedures
SRA	Stringent Regulatory Authority
SSFFs	Sub-standard and Falsified Medicines
TC	Technical Committees
TMDA	Tanzania Medicines and Medical Devices Authority
TWG	Technical Working Groups
UH	University of Hertfordshire
USD	United States Dollar

WAC	West African Community
WAHO	West African Health Organisation
WA-MRH	ECOWAS-WAHO MRH Project
WHO	World Health Organization
WHO WLA	WHO Listed Authorities
ZaZiBoNa	Zambia, Zimbabwe, Botswana, Namibia Collaborative Medicines Regulatory Process
ZFDA	Zanzibar Food and Drugs Authority

CHAPTER 1

GENERAL INTRODUCTION

BACKGROUND

One of the main functions of a medicine regulatory authority is to promote public health and protect the community from any harm (Giaquinto et al., 2020). The review of medical products by regulatory agencies is considered as one of the first steps to access to good-quality and effective medicines (Wang, 2022). Strong medicines regulatory systems and effective coordination will accelerate efforts to improve public health and ensure that African people have access to essential medical products and technologies, but there are several challenges that impede the review and registration of medical products in African countries by pharmaceutical companies (Narsai et al., 2012). African medicines regulatory systems are faced with resource and capacity constraints (Roth et al., 2018), including a lack of harmonised tools that meet international standards to collect, collate, analyse and report on harmonisation efforts results (WHO, 2010).

The Need to Strengthen African Medicines Regulatory Agencies.

A recent study showed that all but one (except for Sahrawi Republic) of the 55 African Union (AU) member states have national medicines regulatory authorities (NRAs) with different structures and level of functionality (Ndomondo-Sigonda et al., 2017). Sub-Saharan African countries have inadequate capacity to regulate medicines due to fragmented legal frameworks and weak management structures and processes, as well as limited human and financial resources. This has led to a proliferation of substandard and falsified medicines (SFs) in various markets in the continent (Rago et al., 2014). According to Ndomondo-Sigonda et al. (2020), of 46 sub-Saharan African countries, only 7% have moderately developed medicine regulatory capacity, while 63% have minimal capacities and the remaining 30% do not have a functional NRA in place (WHO, 2010). Moreover, regulatory systems in Africa may include poor inspection practices; ineffective licensing and product registration systems; inadequate access to quality control laboratories; and non-existent pharmacovigilance, clinical trials oversight and drug promotion control systems; with subsequent 30% product quality failure rates (WHO regional Office for World Health Organization Regional Office for Africa, 2013). Other issues include inadequate regulatory information management systems (RIMS), transparency and accountability as well as widespread conflicts of interest (Ndomondo-Sigonda et al., 2017). Hence, there is a need to strengthen medicines regulatory systems on the continent. One of the approaches is to promote harmonisation work and ensure alignment of different initiatives in the medicines regulatory space to ensure concerted efforts in tackling public health challenges and sustain Pan-African led initiatives.

The aim of this study is to demonstrate how regional medicines regulatory harmonisation programmes may contribute to the effectiveness and efficiency of the AMA using the East African Community Medicines Regulatory Harmonisation (EAC-MRH) programme as a particular example of how key African regulatory entities serve as building blocks for the African Medicines Agency (AMA) and will underpin this major continental initiative. It also highlights the benefits and challenges of medicines regulatory harmonisation based on the EAC-MRH experience that will facilitate an effective and efficient AMA.

AMRH Technical Committees

As part of the alignment of regulatory systems strengthening, harmonisation efforts and networks across the continent, the AMRH has ten continental technical committees (TCs) (Figure. 1.1). They include the African Medicines Quality Forum (AMQF) on quality assurance and post-marketing surveillance; the African Medical Devices Forum (AMDF); the African Vaccines Regulatory Forum (AVAREF) for clinical trials and ethics oversight; Pharmacovigilance (PV); the African Blood Regulators Forum (ABRF); Medicines Policy and Regulatory Reforms (MPRR); Regulatory Capacity Development (RCD) Good Manufacturing Practice (GMP); Evaluation of Medicinal Products (EMP) and Information Management System (IMS). Each TC is composed of regulatory experts from NRAs in Africa who represent their REC as well as collaborative partners.

Regional Economic Communities

The AMRH objectives are to be achieved through harmonisation of medicines regulatory frameworks in the five regions in Africa (Chattu et al., 2021); East African Community (EAC), Economic Community of West Africa States (ECOWAS), the Economic Community of Central African States (ECCAS), Southern African Development Community (SADC), the Intergovernmental Authority for Development (IGAD). The AMRH initiative is being implemented through the Regional Economic Communities (RECs), which are made up of NMRAs that belong to each region. The RECs have established Expert Working Groups (EWG) and/or Technical Working Groups and steering committees at regional levels that are supported technically and strategically by the AMRH Technical Committees and the AMRH Steering Committee, at a continental level. The AMRH Partnership Platform is a partnership of organisations contributing towards the achievement of the AMRH vision. The aim of this platform is to enhance the efficiency and effectiveness in the implementation of the regulatory systems strengthening and harmonisation agenda in Africa, through optimal coordination of

the different partners and stakeholders providing regulatory oversight. The support provided by partners could either be financial, technical and/or advocacy.

Figure 1.1 AMRH Technical Committees.

Economic Community of West Africa States

Medicines are inaccessible for the majority of West Africans. This inaccessibility contributes to the persistence and spread of diseases in the ECOWAS region. Although production capacity exists in the region, most of the medicines are still imported. Launched in 2017, the objective of the West Africa Medicines Regulatory Harmonisation (WA-MRH) programme is to improve access to essential medicines, vaccines and other health products (Owusu-Asante et al., 2022). There are 15 countries in the ECOWAS region all of whom are participating in the WA-MRH programme (Benin, Burkina Faso, Cape Verde, Gambia, Ghana, Guinea, Guinea-Bissau, Ivory Coast, Liberia, Mali, Niger, Nigeria, Senegal, Sierra Leone and Togo).

Economic Community of Central African States

All seven countries in the ECCAS are active participants in the ECCAS-MRH programme (Cameroon, Central African Republic, Chad, Congo-Brazzaville, Democratic Republic of Congo, Equatorial Guinea, and Gabon). The ECCAS-MRH is being coordinated by the ECCAS body responsible for public health issues, the Coordination Organization for the Fight Against Endemics in Central Africa (OCEAC). The OCEAC leads the process of harmonising national pharmaceutical policies in Central Africa. To date, joint activities (joint reviews of marketing authorisation dossiers), training sessions and advocacy, are carried out in the ECCAS zone, in collaboration with partners**.**

Southern African Development Community

The SADC region is composed of 16 countries (Angola, Botswana, Comoros Islands, Democratic Republic of Congo, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Eswatini., United Republic of Tanzania, Zambia, and Zimbabwe. The ZaZiBoNa initiative was created by four countries (Zambia, Zimbabwe, Botswana and Namibia) in 2013 to address the challenges of medicines regulation faced by NMRAs in the SADC region. These include a high backlog of applications submitted for regions in the agencies, high staff turnover, long registration timelines, inadequate financial and human resources and a lack of capacity to assess some products (Sithole et al., 2020). As of 2018, the ZaZiBoNa scheme had 11 participants from the SADC member states. These include Botswana, Democratic Republic of Congo, Mozambique, Namibia, South Africa, Zambia, Zimbabwe, Angola, Malawi, Seychelles and Eswatini. Current developments in the SADC region involve a decision to implement the SADC-MRH project. Ministers in the region selected the Medicines Control Authority of Zimbabwe (MCAZ) to facilitate the implementation of the project.

Intergovernmental Authority for Development

The IGAD is composed of eight countries who all participate in the IGAD-MRH programme (Djibouti, Eritrea, Ethiopia, Kenya, Somalia, South Sudan, Sudan, Uganda). However, three of these countries (Kenya, South Sudan, and Uganda) also belong to the EAC region and participate in both programmes. The IGAD-MRH programme promotes the harmonisation of medicines registration in the region, which is a key contributor to public health and leads to the rapid access to good-quality, safe and effective medicines for priority diseases. The project

is organised in sections that includes medicines registration, good manufacturing practice and quality management systems.

THE EAC-MRH PROGRAMME

History

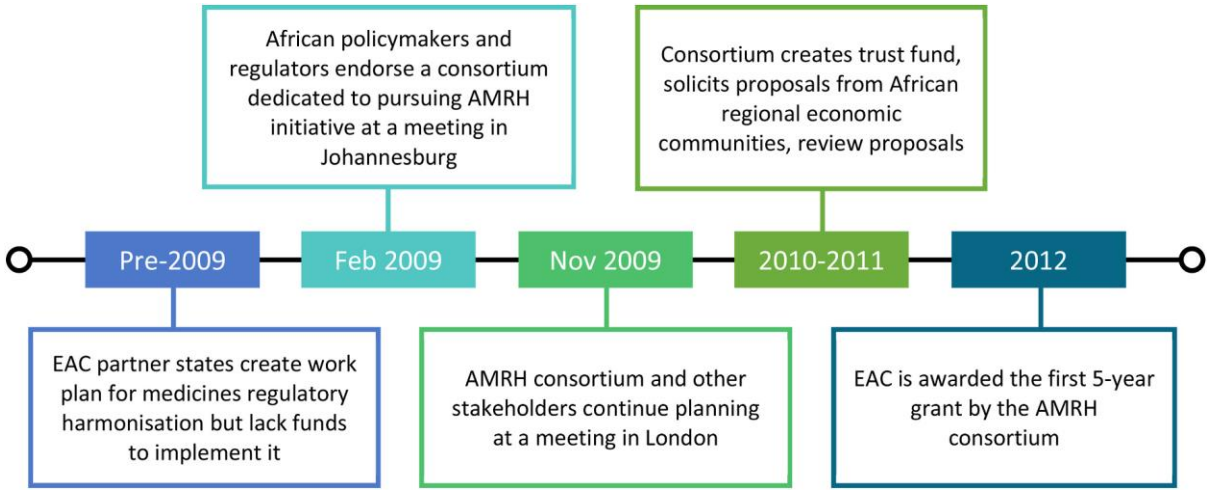
After the establishment of the AMRH initiative in 2009, a consortium was created by African policy makers and regulators to spearhead the activities of the AMRH initiative (WHO, 2014). In 2009, the consortium decided to implement the programme with the registration of generic medicines through the African RECs (Figure. 1.2). The RECs were therefore requested to develop project proposals in 2010/2011. Finances from the AMRH Trust Fund were only available to support one REC and the EAC was chosen as the pilot REC for five years in 2012. A situational analysis conducted by the AMRH Partners on the status of medicines regulation in the EAC region showed differences in countries' laws and regulations with the NMRAs of the region, such as no mutually recognised legal framework and major disparities in capacity (Kamwanja et al., 2010; Mashingia et al., 2020). To address these challenges, the EAC Secretariat in collaboration with the EAC NRAs established the EAC-MRH project as the regional coordinating body of the AMRH initiative in 2012. This was part of the implementation of one of the provisions of the EAC Treaty, Chapter 21, Article 118 on regional harmonisation in health (EAC Compendium, 2014). This was the first regional harmonisation project and the lessons learned from its pilot phase are being used to scale up regulatory harmonisation in Africa (Ndomondo-Sigonda et al., 2020a) and could be of value in the initiation of harmonisation by the African Medicines Agency.

Objectives Of The EAC-MRH

This regional MRH project aims to facilitate the removal of barriers to scientific research and innovation; efficient and transparent marketing authorization; and the easy procurement of medical products in the region thereby optimizing the pharmaceutical markets. The implementation of the MRH project also aims at minimizing duplication of efforts. This leads to the cost-effective use of limited resources, efficient and effective delivery of regulatory services that will instil transparency and the eminent accountability by all stakeholders (Ndomondo-Sigonda et al., 2020). The initial focus of the project was on registration of generic medical products then to later expand to other medical products and regulatory functions

(Mashingia et al., 2020). The overall goal of the EAC-MRH project is to enhance access to safe, efficacious and quality medicines by patients.

Figure 1.2 Timeline of major events leading to the creation of the EAC-MRH initiative; reprinted from Sillo et al. (2020).



The EAC-MRH project had six initial objectives outlined during the start of the project (Silo et al, 2020) and these were to:

- Implement an agreed common technical document for registration of Medicines in the EAC Partner States
- Implement a common information management system for medicines registration in each of the EAC Partner States' NMRAs which are linked in all Partner States and EAC Secretariat
- Implement a quality management system in each of the EAC Partner States' NMRAs
- Build regional and national capacity to implement medicines registration harmonization in the EAC
- Develop and implement a framework for mutual recognition based on Chapter 21, Article 118 of the East African Community Treaty
- Create a platform for information sharing on the harmonized medicines registration system to key stakeholders at national and regional level.

After the first five years of the project (2012 to 2017), its goals were reviewed as follows as the project's future roadmap for the period 2020 t0 2022 was being created (Arik et al, 2020); these were to:

- Improve existing processes and expand into new regulatory areas and activities
- Develop a well-coordinated and well-functioning regional assessment and inspection process, on which national registration decisions can rely
- Create a sustainable, semiautonomous agency that will provide regulatory guidance and coordination for the entire region by 2022

The key milestones for the second phase of the EAC-MRH are illustrated in Figure 1.3.

Organisational Structure of the EAC-MRH

Since its inception, the EAC-MRH has had the following governance framework with defined roles and responsibilities for each structure to support the implementation of the project.

The EAC Sectoral Council of Ministers of Health is responsible for setting the overall policy direction of the project. The steering committing approves annual budgets, work plans and is also responsible for technical oversight of the project. The overall project management role is the responsibility of the EAC Coordination Team while the MRH local focal point who are also part of the coordination team are present in each NRA and report to the Head of the NRA. During the implementation of the 2020-2022 Roadmap, Regional Technical Officers (RTOs) have been appointed in each NRA to focus on the facilitation of regional regulatory activities for their NRA (Arik et al, 2022). There also exists the Regional Technical Working Groups who develop the annual work plan, budgets, technical guidelines and procedures.

Technical partners provide technical support while Advocacy and coordinating regional stakeholders and high level political intervention where necessary (Figure 1.4). The Financial management responsibility is no more applicable as the multi-donor trust fund has been dissolved.

Countries Participating in the EAC-MRH Initiative

The East African Community (EAC-MRH) is a regional inter-governmental organization of seven national medicines regulatory authorities (NRAs) consisting of six partner states participating in this initiative; namely the Republic of Burundi, Republic of Kenya, Republic of Uganda, Republic of Rwanda, Republic of South Sudan and the United Republic of Tanzania. The United Republic of Tanzania is composed of Tanzania Mainland and Tanzania Zanzibar (Figure 1.5). The seven NMRAs in this region include: Pharmacy and Poisons Board-PPB, Kenya; National Drug Authority-NDA, Uganda; The Tanzania Medical Devices Authority (TMDA); Zanzibar Food and Drugs Authority (ZFDA) Tanzania; Drug and Food

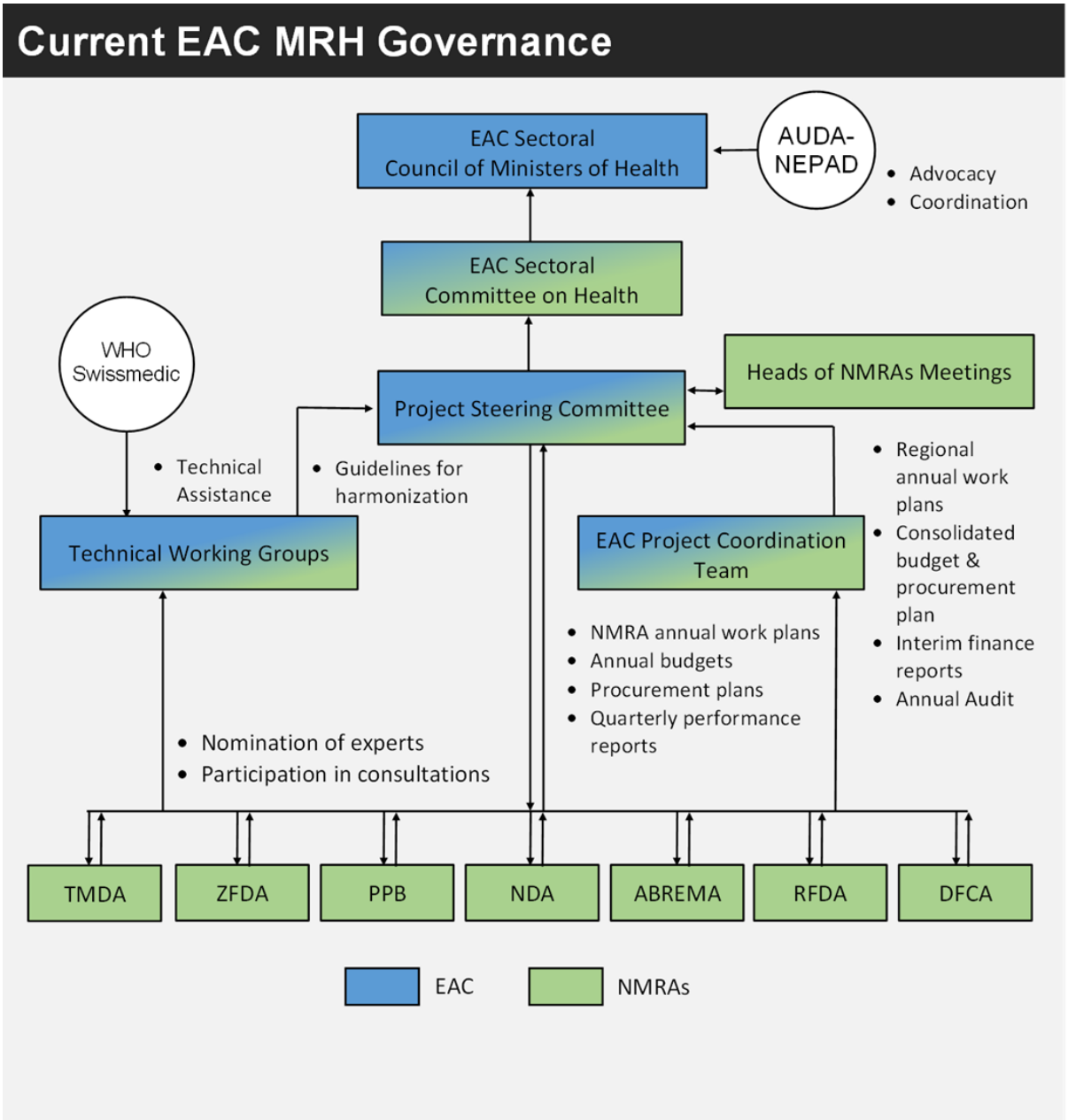
Control Authority –DFCA South Sudan; Burundi Food and Medicines Regulatory Authority (ABREMA) and Rwanda Food and Drugs Authority. These countries share a common history, market, language, culture, and already had a treaty that called for these countries to harmonise.

Figure 1.3 The Roadmap for the Future of the EAC's MRH initiative, 2020–2022

	2020	2021	2022
Improved and extended JA & GMP	• Vaccines within the scope of Joint Assessments • Guidelines for assessing novel IVDs & IVDs added to Joint Assessments		• Jas of at least 10 vaccines and 10 IVDs completed • Guidelines for assessing novel biologics and biosimilars implemented • Guidelines for assessing medical devices adopted
New regulatory functions	• AVAREF guidelines for clinical trials adopted & joint evaluations of multi-country trials begin • PV, lab testing, & CRO inspection guidelines	• PV, lab testing guidelines, & joint PV/lab testing activities • Joint inspections of CROs begin	
Efficiency & effectiveness			• Rwanda, Burundi, and South Sudan achieve ISO 9001:2015 certification • All NMRAs except South Sudan are formally WHO benchmarked
Sustainability mechanisms	• RTOs facilitate regional regulatory activities and provide single point of contract for Joint Assessments & inspections	• Fee-for-service model is in place to support initiatives regional regulatory activities	• Legal authority for an EAC Medicines Agency obtained
Reliance			• Three 1:1 recognition agreements are in place between EAC Partner States
Legal framework			• Binding region-wide mutual recognition agreement drafted
Capacity building	• Newest EAC Partner Sate, South Sudan, is fully integrated into the initiative		

CRO, contract research organization; EAC, East African Community; GMP, good manufacturing practice; ISO, International Organization for Standardization; IVD, in vitro diagnostic; JA, joint assessment; MRH, Medicines Regulatory Harmonization; NMRA, national medicines regulatory authority; PV, pharmacovigilance; RTO, regional technical officer; WHO, World Health Organization.**https://doi.org/10.1371/journal.pmed.1003129.g001**

Figure 1.4 EAC-MRH Governance Framework



Scope of Products for the EAC-MRH

In 2012 when the EAC-MRH Project was launched, the initial focus of the project was on registration of generic medical products then to later expand to other medical products and regulatory functions (Mashingia et al., 2020). The EAC-MRH has however expanded its scope to applications submitted to at least two NMRAs, biotherapeutics, biosimilars, applications that are not WHO Prequalified and all medicinal products.

Figure 1.5 Map of East African Community

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

According to the EAC-MRH Expression of Interest published in June 2020, the EAC-MRH has the following priority list medicines for managing certain medical conditions.

- Medical conditions with regards to maternal, neonatal and children health
    - HIV, malaria, tuberculosis, reproductive and neurological disorders
    - Neglected diseases: leishmaniasis, pneumocystosis and toxoplasmosis, filariasis, and strongyloidiasis
    - Cancer, diabetes, hypertension, kidney, hepatic, and neurological conditions
- Prescription Medicines from Domestic Manufacturers within the EAC region
- Biotherapeutics Products and Biosimilars

Successes of EAC Harmonisation

Through the AMRH, the EAC has developed and implemented the Medicines Regulatory Harmonisation project that has enabled member states to harmonize technical requirements and standards, jointly assess applications and inspect manufacturing sites, and streamline decision-making processes. Over a decade, several successes have been recorded by this work sharing

initiative. Countries in this region have developed harmonized guidelines for the regulation of medical products. The harmonised guidelines for the EAC medicines regulation became effective from January 2015. In 2018, a Cooperation Framework Agreement for the NRAs of EAC Partner States was approved by the EAC's Council of Health Ministers. A compendium has been developed on medicines evaluation and registration with established Common Technical Documents (CTD) to provide harmonised medicines registration procedures ((EAC Secretariat, 2014) to applicants. According to Keyter et al (2020), the implementation of CTD helps in supporting reliance and recognition efforts. The initiative aimed to have about three one on one bilateral recognition agreements in place by 2022 and a draft regional mutual recognition agreement (Arik et al, 2020). Between 2017 and 2021, three new semi-autonomous agencies Rwanda FDA (2018), Burundi (ABREMA, 2021), and Zanzibar (ZFDA, 2017) during the project life have also been established in the region thanks to this initiative. Timelines for registration of medical products have also decreased by almost half (Ndomondo-Sigonda et al,2020). Between 2012 and 2017, the registration timelines decreased in NRAs from 24 months to 8 to 14 months on average. Since 2015, the initiative began conducting Joint assessments of dossiers and joint inspections of manufacturing sites). By 2020, about 10 joint assessments had been conducted with about 83 products reviewed and 36 recommended for registration by the EAC Partner States (Mashingia et al., 2020). As of February 2022, 24 Joint GMP Inspections have been conducted in Africa, Asia, Europe and USA and all sites compliant to EAC GMP Standards. One hundred and eighty-seven applications received for joint scientific review out of which 184 applications have been jointly assessed, 89 medical products approved for marketing authorisation and 95 applications under different levels of the review process. As of February 2024, 29 Joint assessments and 54 joint GMP Inspections have been conducted. 254 applications received for joint scientific review out of which 249 applications have been jointly assessed, 140 medical products approved for marketing authorisation and 114 applications under different levels of the review process

The median time for joint scientific review, submission to end of assessment for all products takes 53 to 221 working days; regulator's time is between 44-391 working days while manufacturers' time to answer queries is 5-927 working days. An Integrated Information Management System and Programme Website has been developed– www.eac.int/mrh. Four EAC NMRAs (TMDA, ZFDA, PPB and NDA) are now ISO 9000:2015 Certified. (EAC-MRH 2022).

Challenges

AU Member States and RECs are making significant efforts to strengthen and harmonise the medicines regulatory systems by implementing programmes under the AMRH initiative (Ndomondo-Sigonda et al., 2018) despite challenges.

Legal position

The EAC-MRH initiative does not have a legal framework to support its operations. Rather than wait to establish a regional medicines agency, the member states in the region decided to rely on decisions made during the joint assessment and joint inspection activities. The reliance here by NRAs when making national decisions is based on mutual trust and respect rather than a legal framework. To keep all NRAs actively involved in this initiative, they have been assigned leadership roles based on their areas of expertise in each regulatory function ((Ndomondo-Sigonda et al., 2020). Several studies (BCG, 2017; Mashingia et al., 2020; Ncube et al., 2021) have identified that major challenges faced by EAC-MRH initiative are due to the lack of a clear legal framework by the EAC-MRH.

Resource and capacity

Resource and capacity constraints, as well as weak and fragmented legal frameworks are key challenges that have hindered the achievement of the EAC-MRH initial project objectives. There is limited technical and institutional capacity at both regional and national level (Arik et al., 2020). Different capacities of NMRAs affect trust, as sometimes the more resourced agencies tend not to trust the decisions of the newer agencies in the region; harmonisation has also limited the capacity of the less mature agencies to specialise or improve as they tend to rely on the mature agencies instead of building their own capacity (Mashingia et al., 2020).

Finances

A study of NMRA financial sustainability in the EAC by Ndomondo-Sigonda and associates (2020), shows that one of the major factors hindering efficient medicine regulation in the EAC is the insufficient financial resources at both the national and regional level. This study shows that the main funding source of the agencies were from industry fees, followed by government subventions and donor funds being the least. The source of funds from industry fees and government were classified as sources that will enhance financial sustainability (Ndomondo-Sigonda et al., 2020b)

Country processes

There are inconsistent regulatory processes and variable technical standards and guidelines between countries that do not meet international standards (Ncube et al., 2021). Other highlighted barriers (Mashingia et al., 2020) are a lack of a binding legal framework amongst the member states in the EAC; understaffing and high staff turnover; less involvement of the Heads of Agencies in shaping the agenda of the harmonisation project; and delays in products being registered at the national level after the regional approval has been made. Submission of applications and payment of fees by manufacturers again to NMRAs even after the joint review processes has been completed, only further delay registration timelines.

Tracking systems

A lack of transparency, especially in providing clear timelines, means that applicants are unable to track applications, NRAs and applicants are not being able to follow up on each other's questions, resulting in delays by NRAs in registering products after a joint recommendation has been made. This poor communication between assessors was also highlighted in other studies (Mashingia et al., 2020; Ngum et al., 2022.

Review template

Despite the very high death rates in Africa due to non-communicable disease, out of the 55 countries in Africa, only South Africa has a clear framework on regulation of biosimilars (Rathore and Bhargava, 2021). The EAC-MRH still mainly focuses on the review of generics and has evaluation report, query, and screening templates for these reviews; however, it has drafted a guideline on pharmacovigilance (Mashingia et al., 2020).

Submission process

Studies also show that there is a reluctance from companies manufacturing medical products to register their products in African markets, which is also a major factor delaying access to medicines (Sillo et al., 2020). This reluctance is due to the lengthy application process and the time, expense, and effort needed for the registration process in each NMRA (Sillo et al., 2020). Another reason cited by Mashingia et al. (2020) is that manufacturers sometimes decide not to register the products in all the member states, even after a regional decision has been made.

Although three months is the target timeline for registration of recommended medical products by the NMRAs, not all products are registered in all the member states at the stipulated time for various reasons. According to the EAC joint assessment pathway, the manufacturer is

expected to apply for registration of a product to NMRAs of interest after the regional decision is made. Some manufacturers may decide not to register their products in some countries and sometimes, the applicant may not be ready to market their products in a particular country (Mashingia et al., 2023).

DISCUSSION

Disease Burden in Africa

The African population suffers from a high disease burden (Micklesfield et al., 2022). There is a rapid increase in infectious and non-communicable disease due to the increase in urbanisation, demographics and demographic transition in Africa (Cappuccio and Miller, 2016). High disease burden has led to high morbidity and mortality in Sub-Saharan Africa (Mudie et al., 2019). This increase in disease burden is causing further strain on the healthcare systems that are not well equipped to manage such challenges (Juma et al., 2018). Corona Virus Disease (COVID-19), which became a world pandemic according to the WHO, has further exacerbated the situation (Tadesse et al., 2020). What did this mean to Africa with its very fragile health and economic systems, coupled with the already high human immunodeficiency virus, tuberculosis and malaria burden? This novel virus triggered more health and economic challenges to a continent where most of its people live below the poverty level of less than 1.9 $ a day (World Bank). One of the major health and economic challenges is access to health services due to the inability of the vulnerable population to afford medical care or quality, effective and safe medical products, as 70% of the population works in the informal sector with no health insurance and social protection (Lawson-Lartego and Cohen, 2020). This eventually leads to the people consuming sub-standard falsified medicines, which has worsened the health situation and further increased the disease burden (Amimo et al., 2020). The African continent has been exposed during the COVID 19 pandemic and thus revealing the continent's vulnerability in providing access to essential medicines, vaccines and health technologies (Sidibe et al., 2023).

Regional Regulatory Harmonisation Initiative Contribution to Potential Universal Health Coverage by the African Medicines Agency.

One of the determinants of quality healthcare is the availability of an "independent-science based regulation of medical products" (Sillo et al., 2020). An African continental regulatory mechanism for medical products such as the AMA is critical to address the issues of access to essential medical products on the continent. It is the hope of the African Ministers of Health,

based on African Health Strategy (2016–2030) that a strong and efficient AMA will address the inequities and inequalities of health coverage as observed during the COVID-19 era and this has resulted in a call for prioritisation of continental regulation of medical products (Chattu et al., 2021). The AMA is critical in contributing to the achievement of universal health coverage as it will enable access to quality, safe and essential medical products, and vaccines in Africa. The AMA is being established as the main driver to "enhancing regulatory oversight of medicines and vaccines across the continent's 55 countries" Chattu et al., 2021). The COVID 19 pandemic exposed the gaps and inconsistencies in medicines regulation in the 55 countries and five regional harmonisation programmes that this continental regulatory body will need to provide. In providing a service to the African people, the AMA will harmonise the regulation of medical products on the African continent (Chattu et al., 2021). There will not be an immediate change in access to medicines, because the AMA will not replace national medicines regulatory authorities; however, experts say it has the potential to improve efficiency, reduce duplication, harmonise standards and processes to enable comparability, and encourage reliance on tested methods of medicines regulation. The agency will be helpful, as it will enforce centralised regulatory measures by bringing together all the 55 regulatory bodies on the continent. According to expert opinion (Makoni., 2021), the "strength of the AMA lies in the large number of countries in the African Union, the large potential market for medicines, and the existing efforts at regional harmonisation that can be built on by the Agency". If the implementation of the African Continental Free Trade Area is accelerated, it will provide a market of over 1.3 billion people to the pharmaceutical sector. This will, therefore, address the challenge of market size that pharmaceutical companies have had for African countries and more importantly, the AMA will provide confidence in the regulatory ecosystem. This will thus increase the interest of manufacturers to invest in local production of medical products and vaccines in Africa (Sidibe et al., 2023). Therefore, improvement in regulatory science in Africa could also lead to increased local discovery and clinical trial capabilities. The AMA will need to have strong and agile NRAs and REC-MRH programmes and or authorities to be able to address all or most of the regulatory challenges experienced for many years by Sub-Saharan Africa countries. How ready are these entities to embrace the recently established continental agency for medical products regulation?

Adoption of AMRH Workstreams by the African Medicines Agency

The AMA is an outcome of the AMRH initiative (Chattu et al., 2021; Ncube et al., 2021). Efforts are being made for the AMA to capitalise on the existing mechanisms that are already

in place (Ncube et al., 2021). If the AMA adopts the workstreams of AMRH, then this could be a major contribution to its operationalisation, thereby speeding up the approval processes and fast-tracking the availability of medicines to patients in Africa (Chattu et al., 2021). Through the WHO Global Benchmarking Tool (GBT), African NRAs are assessing their capacity and creating institutional development plans that will facilitate regulatory systems strengthening. According to the WHO GBT, an NRA should be able to perform some or all of the nine regulatory functions. These include: national regulatory systems registration and marketing authorization; vigilance; market surveillance and control; licensing establishments; regulatory inspection; laboratory testing; clinical trials oversight; and NRA lot release. The GBT is a five-step approach to capacity development through which NMRAs can measure their strengths and weaknesses and then reach out for support (Broojerdi et al., 2020). The WHO recommends that countries are assessed to determine their maturity levels for each of the above functions as this is vital to understanding the capacity of the authority and the harmonisation and reliance efforts. Due to resources constraints, NMRAs with lower maturity levels can rely on countries with higher maturity levels through the harmonisation scheme as well as the good practices outlined by the WHO. Mutual recognition or cooperation agreement amongst the National Medicines Regulatory Authorities (NMRAs) is key.

Medicines Regulatory Harmonisation Initiatives.

Collaborations and reliance amongst countries is being facilitated by the AMRH Initiative through the regional harmonisation programs (AU Press release, 2021). In the post-COVID era, it is imperative to also strengthen regional initiatives as they work toward addressing the challenges that still prevail (Chattu et al., 2021). Given that the AMA will only regulate 5% of products, which will be considered as priority or essential medicines and complex molecules, it will not replace the NRAs or RECs but will rather complement their work. According to Article 4 of the AMA Treaty, the main objective of the AMA will be "to enhance the capacity of State Parties and RECs to regulate medical products in order to improve access to quality, safe, and efficacious medical products on the continent". Therefore, the RECs who draw expertise from NRAs will be the pillars of the AMA.

Article 30 of the AMA Treaty specifies that AMA will establish a relationship with other organisations and institutions, especially those that will assist AMA to achieve its objectives. Given that duplication needs to be minimised, the AMA will rely on the decisions of the WHO-

listed regulatory authorities as well as well-resourced regulatory authorities like the EMA and US FDA as well as the WHO Prequalification.

Continental Technical Committees

The ten continental TCs established by the AMRH initiative are key to the success of the AMA, as they are already performing some AMA related functions outlined in article 6 of the AMA Treaty. Through the African Vaccines Regulatory Forum TC, the AMA can serve to unlock clinical research in Africa by enhancing the continent's contribution to clinical trials and innovation (Hwenda et al., 2022). The AVAREF is also coordinating joint reviews of applications for conducting clinical trials in Africa. The AMA can build regulatory capacity of NRAs through the eleven AMRH Regional Centres of Regulatory Excellence (RCOREs) established within the Regulatory Capacity Development TC (Chattu et al., 2021). To build capacity, a pool of regulatory experts on the continent is being established by the AMRH. This will also be one of the assets for AMA once it becomes operational. According to the AMA Treaty, enhancing optimal use of limited resources, a pool of regulatory expertise will enable capacities to strengthen networking. Also, the AMA as part of the treaty, is expected to provide technical assistance on regulatory matters to the national regulatory authorities as well as the regional initiatives. The AMA is also expected to bring technical expertise and shared financial and human resources to address the inadequate reporting of adverse effects and poor post-marketing surveillance which has led to the availability of SF medical products in the market. The pharmacovigilance and African Medicines Quality Forum TCs are already working towards addressing some of these challenges. The groundwork laid by the Evaluation and Medicinal Products TC will assist the AMA to expedite medicines' delivery on the continent and will encourage the sharing of regulatory information that will be beneficial to science (Chattu et al., 2021). This information can be shared through the Regulatory Information Sharing Portal that is currently being developed by the Information Management System TC. This portal will assist the AMA in sharing information that will facilitate the usage of the most appropriate and effective medical products in a timely manner. Information availability has been a key challenge for the harmonisation initiative (Chattu et al., 2021; Ngum et al., 2022). Another function of the AMA is to coordinate the inspection of drug manufacturing sites and this work has already commenced through the development of a Compendium of standard operating procedures for GMP inspections for biological manufacturing facilities and other priority products and a continental reliance framework by the GMP TC.

African Medicines Agency to Learn Lessons from the European Medicines Agency Best Practices.

It is expected that the AMA will adapt or adopt some best practices from the European Medicines Agency, which over the years has acquired a wealth of experience by spear heading the scientific evaluation of innovative and high-technology medicines developed by pharmaceutical companies for use in the European Union. Accordingly, the EMA is represented as a member of some of the AMRH technical committees. All EU member states are mandated to implement the decision from the centralised procedure. In the case of the AMA, member states are not mandated to implement the recommendations from AMA joint review outcomes. Once functional, it may be anticipated that the AMA may experience a similar delay in the registration of products due to lack of a legal mandate faced by the EAC-MRH. Similar to the EMA Committee for Medicinal Products for Human use (CHMP), the AMRH has established the Evaluation of Medicinal Products (EMP) Technical Committee as one of the workstreams that the AMA can leverage to conduct scientific assessments of complex molecules and priority products for the continent.

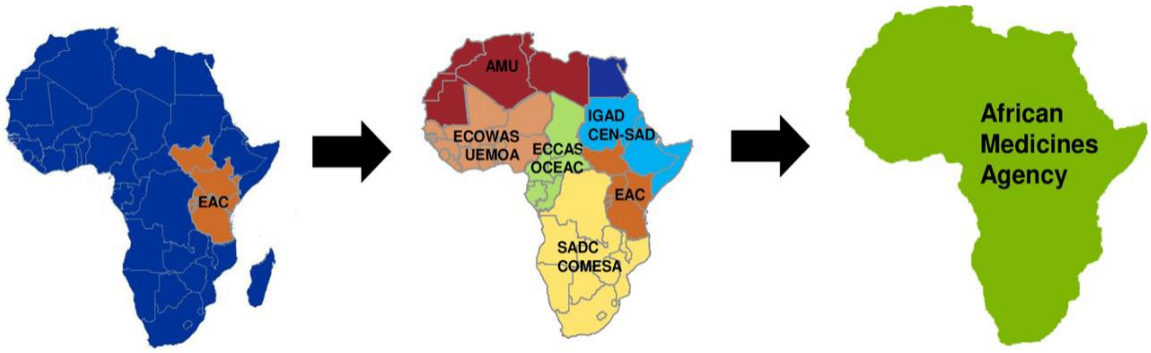
Boosting Ratification of African Medicines Agency Treaty by More Countries

Although the main objective of the AMA is to enhance capacity of state parties and RECs to regulate medical products to improve access to quality, safe, and efficacious medical products on the continent, universal access cannot be achieved without the inclusivity of all countries. No country must be left behind, as every human being has the right to health care despite the status of being a state party to AMA or not. It will be problematic if the AMA only serves the countries that have ratified the Treaty, as movement of substandard and falsified medicines will continue through the porous borders (Jerving, 2022). The AUC, AUDA-NEPAD and Partners are therefore working tirelessly to encourage all the countries to ratify the AMA Treaty so that everyone in Africa can enjoy the benefit of this continental Agency. In 2020, the AUDA-NEPAD developed a country engagement plan to guide advocating for the ratification of AMA Treaty and to encourage the remaining countries to sign and ratify the AMA Treaty so that it could come into force. Currently, the guidance notes developed are being used to support NMRAs with their in-country ratification processes. Targeted workshops are being organised, especially with countries that have shown an interest and those that have well-resourced NRAs. A special envoy has also been assigned to engage political leaders of targeted countries to fast track the ratification process. All 55 countries in Africa are expected to be part of the AMA. Another approach as mentioned by Okonji (2022) to

encourage more countries to ratify the AMA Treaty is to support member states, that have signed the Treaty to serve as "AMA Goodwill Ambassadors" who can inspire and advocate for the ratification of the Treaty by sharing AMA benefits at the national, regional and continental levels.

The strength of the EAC-MRH initiative and all the REC-MRH projects is key in the operationalisation of the African Medicines Agency (AMA) which was established on 05 November 2021 (Figure 1.6).

Figure 1.6 The EAC and other harmonisation Initiatives in Africa are the pillars to the AMA (Source: Ndomondo-Sigonda et al, 2020)



CONCLUSIONS

The overall benefit of the EAC-MRH program is to streamline the regulatory approach where there is one submission, one scientific review and one recommendation applicable to all partner states, with less cost to the pharmaceutical industry and regulatory authorities, including efficiency and a reduced time to marketing authorisation as well as a lack of duplication of efforts. With ten years of experience of the EAC-MRH work-sharing initiative (2012–2022), this is the right time to develop the next "Roadmap for the Future of the EAC-MRH initiative" (2023–2028) in this new African Medicine Agency era. It is hoped that the AMA will build on the successes of these regional initiatives while addressing most of the shortfalls experienced by the NRAs and the regional harmonisations programmes. If the achievements of AMRH are used as assets, then these can make a major contribution to the operationalisation of the African Medicines Agency.

SUMMARY

- The purpose of this chapter was to demonstrate how regional medicines regulatory harmonisation initiatives may contribute to the effectiveness and efficiency of the African Medicines Agency (AMA) focussing on the East African Community Medicines Regulatory Harmonisation (EAC-MRH) programme.

- Countries in this region have developed harmonized guidelines for the regulation of medical products and a compendium has been developed on medicines evaluation and registration with established Common Technical Documents (CTDs)

- As part of the alignment of regulatory systems strengthening, harmonisation efforts and networks across the continent, the AMRH has established ten continental technical committees as part of the preparation of the operationalisation of the AMA

- The regional initiatives have experienced a number of challenges including the lack of a legal framework as well as of a tracking system to enhance transparency. Resource and capacity constraints are still major setbacks for this work sharing initiative. The countries in the region still have inconsistent regulatory processes and variable technical standards and guidelines, understaffing and high staff turnover.

- The African Medicines Agency is being established as the main driver for "enhancing the regulatory oversight of medicines and vaccines across the continent's 55 countries"

- The main objective of the AMA will be "to enhance the capacity of State Parties and RECs to regulate medical products in order to improve access to quality, safe, and efficacious medical products on the continent".

- Therefore, it is critical to evaluate the regulatory review systems in the East Africa Community as it contributes to the establishment of the African Medicines Agency.

AIM

Assess the status of medical products regulation in the East Africa Partner States with a view to improving harmonisation and enhancing the regulatory evaluation processes and patients' access to medicines.

OBJECTIVES

- Demonstrate how regional medicines regulatory harmonisation programmes may contribute to the effectiveness and efficiency of the AMA using the East African Community Medicines Regulatory Harmonisation (EAC-MRH) programme
- Evaluate and compare the good review practices, the review models and approval timelines of agencies participating in the East African Medicine Regulatory Harmonisation Initiative
- Evaluate the effectiveness and efficiency of the East African Community Joint Assessment Procedure by Member Countries and pharmaceutical companies .
- Comparison of the three regional medicines regulatory harmonisation Initiatives in Africa, EAC, ECOWAS and SADC .
- Develop a proposed new improved model for the EAC-MRH Initiative

CHAPTER 2

STUDY RATIONALE AND METHODOLOGICAL FRAMEWORK

STUDY RATIONALE

Assessing the performance of regulatory systems' strengthening and harmonisation efforts in Africa requires urgent attention. Therefore, evaluation of the East African Community (EAC) regional harmonisation initiative and proposing possible improvements to the regional review will be a key output for this research. In the introductory chapter, the need for regulatory systems strengthening amongst the African medicines regulatory agencies through regional harmonization has been described. The five medicines regulatory harmonization initiatives being implemented in Africa as an approach to promote harmonisation work and ensure alignment of different initiatives in the medicines regulatory space has also been described. However, the main focus in this chapter has been on one of the regional initiatives, the EAC. Its history from inception, objectives, organizational structure, the scope of products reviewed, operating model, successes and challenges of the EAC-MRH have been outlined. This second chapter is aimed at presenting the study rationale and purpose for conducting this research. It will also fully describe the appropriate methodological framework for this research project.

Based on several articles published on the EAC's Medicines Regulatory Harmonization (MRH) initiative, this research will focus on evaluating the regulatory review systems in the EAC with a view to improving the review process and patients' access to medicines. The research will also demonstrate how the EAC-MRH will contribute to the operationalization of the recently establishment African Medicines Agency (AMA).

The special collection of five articles published in PLOS Medicine about the EAC-MRH Initiative has one of the articles describing the achievements of the initiative over its eight years of existence (Mashingia et al, 2020). However, this research will be the first to provide an evaluation of the regulatory review systems of the EAC-MRH initiative in its current state and after ten years of existence. Furthermore, it will also be the first to evaluate the good review practices and review models implemented by the national regulatory agencies of the EAC. The regulatory review processes of these agencies will be compared especially as they contribute to the assessments and GMP inspections of the EAC-MRH initiative. To assess the effectiveness and efficiency of this initiative, the research will obtain the views of the national regulatory agencies and pharmaceutical industry who have used the initiative to assess their applications and register the products. This research will also be the first to compare three of the regional medicines regulatory harmonization programmes in Africa, namely East, Southern and West African Community-MRH, with the aim to identify best practices and lessons learned.

The following studies will be conducted for this research based on the literature reviewed and study rationale:

- An overview of the EAC-MRH initiative focusing on the history of the initiative, its objectives, scope, progress to date and its potential contribution to the newly established African Medicines Agency
- An evaluation and comparison of the good review practices of countries participating in the EAC joint assessment (Study 1).
- An evaluation of the Review Models and Approval Timelines of Agencies participating in the East African Medicine Regulatory Harmonisation Initiative (Study 2)
- An evaluation of the effectiveness and efficiency of the East African Community Joint Assessment Procedure by Member Countries (Study 3).
- An evaluation of the effectiveness and efficiency of the East African Community joint assessment procedure by pharmaceutical companies (Study 4)
- Comparison of the Three Regional Medicines Regulatory Harmonisation Initiatives In Africa, EAC, ECOWAS and SADC (Study 5).
- Development of a proposed improved model for the EAC-MRH Initiative.

Research Plan

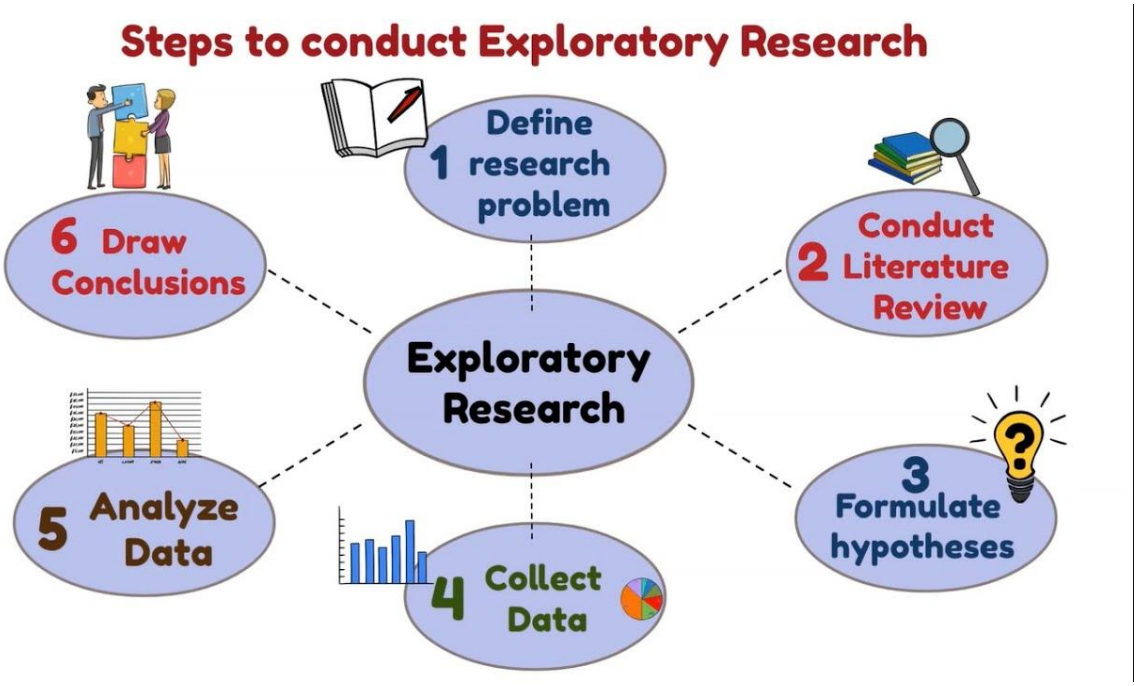
This research will apply combination of exploratory, descriptive, explanatory and evaluative methods. The exploratory method will examine the research questions that have not been studied in depth and are novel. This method will help the researcher to understand more about the medicine's regulation processes in the East African countries. Exploratory research will help to narrow down this research to avoid broadening the scope. Here, data will be collected directly from primary sources who are the participants in the study by administering questionnaires, focus group discussions and conducting interviews. Secondary data will be collected mainly through literature review. Furthermore, explanatory research (Figure 2.1) will also be utilized to facilitate an understanding of the review processes (Tegan,2023) and also to obtain the views of participants on the strengths and weaknesses of the medicines regulation harmonisation initiatives.

The descriptive research method will be used to capture information on review timelines, models and practices. It will help to answer the how, the what and the why questions in the study. The descriptive method will help the researcher to get complete and accurate information from the study by clearly defining what has to be measured and how it will be measured.

Through this method the population under study will be clearly defined through analysis of secondary data, administering questionnaires, and engage participants through panel/focus group discussions, interviews and observing how joint review sessions are conducted (Tegan, 2023).

Another study design that will be employed in this research will be the evaluative research method especially as the main output of this study is to propose strategies for improvement based on an assessment to identify challenges that will inform decision making (Patton, 2023).

Figure 2.1 Steps to conduct Exploratory Research



Source: Tegan, 2023 (Uploaded: Mar 29, 2023)

METHODOLOGICAL FRAMEWORK

Study design

The study design selected will ensure that the research methods utilized to collect and analyse data are sufficient and suitable for the research questions. The design should enable logical and scientific conclusions from the study and ensure that the research questions are answered through empirical data collection, and the goal of the research achieved, whilst appropriate study designs will be implemented in the pursuit of such objectives. Selection of the study design will be based on available resources and the research questions (Ranganathan & Aggarwal, 2018).

Methodological choices

The methodology decided for this research project is a combination of qualitative and quantitative research methods. Qualitative research which entails the collection of non-numeric data, will generate descriptive data. It will be a relevant method to pursue medical products regulation which is one of the public health interventions to improve access to safe, quality and effective medical products. Participants will be recruited to share information in small groups especially on issues regarding the proposed strategies for improvement of medicines regulation in the region. The focus group will enable–responses regarding context and nuances. The researcher will also use semi-structured interviews to ask the same questions to participants on a one-to-one basis. Semi-structured interviews will provide opportunities for the respondent to provide additional information they were not asked by the researcher and confirm the accuracy of their questionnaire responses. The research will also use observational method where the researcher will attend the EAC joint assessments to observe how the joint assessments sessions are being conducted. The following points show how the qualitative research methodology will be used for this research.

- In chapter 1 which gives an overview of the EAC-MRH initiative, a systematic search and narrative literature review will be conducted to obtain the history of the initiative, its objectives, scope, progress to date and its potential contribution to the newly established African Medicines Agency
- A validated established questionnaire, Optimising Efficiencies in Regulatory Agencies (OPERA) (McAuslane et al., 2009) will be used in:
    - Study 1, to evaluate and compare the good review practices of countries participating in the EAC joint assessment in terms of organisation of the regulatory authorities, key milestones in the review process, good review practices and quality decision-making practices and,
    - Study 2, to evaluate the review models and approval timelines of agencies participating in the East African Medicine Regulatory Harmonisation Initiative in terms of; review models used for scientific assessments and data requirements.
- For Study 3, a questionnaire will be developed and validated to obtain the views of the regulatory agencies on the effectiveness and efficiency of the EAC-MRH Initiative.

- For Study 4, a questionnaire will be developed and validated to obtain the views of the pharmaceutical industry on the effectiveness and efficiency of the EAC-MRH Initiative.
- For Study 5, the outcomes of the studies 3 and 4 will be compared with that for the Southern African Community Regional Initiative (ZaZiBoNa) and the West African Community (WAC)-MRH initiative.

The quantitative research method will also be used where numeric data will be collected and analysed and presented as tables and graphs. Overall summaries of the study variables will be made through quantitative research on:

- Study 2 to evaluate the review models and approval timelines of agencies participating in the East African Medicine Regulatory Harmonisation Initiative in terms of; Metrics on NASs, generics, and WHO Prequalified Generics; Mean Approval Times; Review models employed and target timelines and targets for key milestones in the review process.

Study participants

This research project is comprised of five studies and four of these studies will require study participants. Table 2.1 shows the list of study participants that will be recruited throughout this research project.

Table 2.1: Study Participants

Study	Study Participants
Study 1 An evaluation and comparison of the good review practices of countries participating in the EAC joint assessment.	QUESTIONNAIRE • Pharmacy and Poisons Board (PPB), Republic of Kenya • National Drug Authority Uganda (NDA), Republic of Uganda • Rwanda Food and Drugs Authority (Rwanda FDA), Republic of Rwanda • Burundi Food and Medicines Regulatory Authority (ABREMA), Republic of Burundi • Drug and Food Control Authority (DFCA), Republic of South Sudan • Tanzania Medicines and Medical Devices Authority (TMDA) and Zanzibar Medicines and Medical Devices Authority (ZMDA) of the United Republic of Tanzania**.**
Study 2 An evaluation of the Review Models and Approval Timelines of Agencies participating in the East African Medicine Regulatory Harmonisation Initiative.	QUESTIONNAIRE • Pharmacy and Poisons Board (PPB), Republic of Kenya • National Drug Authority Uganda (NDA), Republic of Uganda • Rwanda Food and Drugs Authority (Rwanda FDA), Republic of Rwanda • Burundi Food and Medicines Regulatory Authority (ABREMA), Republic of Burundi • Drug and Food Control Authority (DFCA), Republic of South Sudan • Tanzania Medicines and Medical Devices Authority (TMDA) andZanzibar Medicines and Medical Devices Authority (ZMDA) of the United Republic of Tanzania**.**
Study 3	QUESTIONNAIRE

An evaluation of the effectiveness and efficiency of the East African Community Joint Assessment Procedure by Member Countries.	• Pharmacy and Poisons Board (PPB), Republic of Kenya • National Drug Authority Uganda (NDA), Republic of Uganda • Rwanda Food and Drugs Authority (Rwanda FDA), Republic of Rwanda • Burundi Food and Medicines Regulatory Authority (ABREMA), Republic of Burundi • Drug and Food Control Authority (DFCA), Republic of South Sudan • Tanzania Medicines and Medical Devices Authority (TMDA) and • Zanzibar Medicines and Medical Devices Authority (ZMDA) of the United Republic of Tanzania**.**
Study 4 An evaluation of the effectiveness and efficiency of the East African Community joint assessment procedure by pharmaceutical companies.	QUESTIONNAIRE • Intas Pharmaceutical Limited • Bayer • Cipla Quality Chemical Industries Limited • Dafra Pharma GmbH • Impact RH360 • Laboratoire Aguettant • Laboratory & Allied Ltd • Prodigy Healthcare Limited • Universal Corporation Limited • La Renon Healthcare Pvt. Ltd 9 (India) • Novartis South Africa • F. Hoffmann-La Roche Ltd. • Cipla Ltd • AMRING FARMA SRL, ROMANIA
Study 5 Comparison of the Three Regional Medicines Regulatory Harmonisation Initiatives in Africa- EAC, ECOWAS and SADC	QUESTIONNAIRE (already recruited study participants) • All seven members of the EAC MRH (Burundi, Kenya, Rwanda, South Sudan, Tanzania, Uganda and Zanzibar) as well as all nine active members of the ZaZiBoNa/SADC MRH (Botswana, Democratic Republic of Congo, Malawi, Mozambique, Namibia, South Africa, Tanzania, Zambia

	and Zimbabwe) and all seven members of the ECOWAS MRH (Burkina Faso, Cote d'Ivoire, Ghana, Nigeria, Senegal, Sierra Leone and Togo)

Time horizon

According to Saunders et al. (2019), the time horizon defines the time that will be used to conduct the study. This could either be a cross sectional of short-term study where data collection is carried out within a specific period just once. The other type is the longitudinal study where data is collected repeatedly over a long period with the aim to compare the information obtained. The time horizon for such a study is critical as decisions taken and conclusions made from the outcomes, reflect a specific time period (Dyckhoff & Kasah, 2014).

For this research, a cross sectional study approach will be used to allow the researcher to collect information during a given time frame to achieve the aim and objectives of this research. It will allow comparisons of different variables for a given period. A retrospective approach will be used to collect and analyse data on metrics of applications received and registered; review models, the extent of scientific assessment and data requirements and targets of key milestones in the regulatory review process of the member countries of the EAC-MRH region (2021-2023).

Data Sources

Public domain sources

A literature search will be conducted using the following bibliographic databases, PubMed, Google Scholar, SCOPUS, textbooks and open access theses. To search for information and guidelines, the websites for AUC, AUDA-NEPAD, NRAs, EAC-MRH, EMA, University of Hertfordshire library will be utilized. Presentations and reports made during regulatory conferences and meetings will also be used to extract relevant information for this research.

Sampling techniques

A selection of informants or participants for a study is critical as this determines the achievement of the expected outcome or objectives of the study. A poor selection of participants for a study will risk the integrity of the entire project. Sampling are the elements selected in a population to participant in a study because they meet the criteria for the study (Datta, 2018). Participants for four studies (i.e. 1-4) will be recruited from national regulatory authorities in the EAC region as well as pharmaceutical companies that have submitted their applications to the EAC-MRH Initiative. Since this research will obtain views of the member countries on the EAC-MRH initiative and assess the national regulatory systems for medicines in the region, senior officers heading the respective medicines registration departments of the

authorities will be recruited into the study. Individuals responsible for the regulatory departments in the pharmaceutical companies will also be selected.

According to Datta (2018), there are two types of sampling: 1) Probability sampling methods and 2) non-probability sampling methods. Probability sampling methods also known as random or representative sampling from the sampling frame which entails each member of the population having a chance of being selected for the study. Here, the population needs to be precisely defined. Non-probability sampling methods also known as judgment or non-random sampling means no random selection is made and the elements/participants do not have equal chances of being selected.

There are several types of non-probability sampling techniques; volunteer sampling; convenient sampling; purposive sampling; quota sampling (proportional and non-proportional); snowball sampling; matched Sampling; and genealogy-based sampling (Tongco, 2007). Informant selection for any studies is crucial as these are the people who will provide the information relevant for the studies to enable a researcher to obtain conclusions from the study.

The sampling considered for this research will be neither probability nor non-probability technique because the whole of the sampling frame will be recruited into the study, that is senior officers heading the respective medicines registration departments of the individual authorities of the EAC-MRH member countries. However, reliability and competence of these experts is key and must be ensured and they must meet the pre-defined inclusion and exclusion criteria. The experts should have the knowledge and experience and are willing to participate in the study (Tongco, 2007).

As regards study 4, a random number of generic and ethical (R & D) companies will be recruited to take part in the study.

Data Collection Techniques

The data collection techniques have been considered to ensure that the research aim and objectives are achieved. Based on the considerations of the applicability, practicality, reliability, strengths and weaknesses of alternative data collection techniques, the qualitative and quantitative approaches were selected for this research project as they were deemed most appropriate. Below is a detailed description of the methods selected.

Literature review: Systematic and narrative

To ensure that the research is conducted appropriately, a comprehensive and critical literature review will be carried out. The scope and parameters of the review will be clearly defined as per the following themes or groupings; to gain understanding of the regulatory landscape in the African continent; explore the need to strengthen African medicines regulatory agencies through medicines regulatory harmonisation; describe the history and operating model of the EAC-MRH Initiative and how it will contribute to the operationalisation of the AMA. Through exploratory search a critical evaluation will be conducted from other studies on how the regional medicines regulatory harmonization initiatives are improving regulatory reviews in the national regulatory agencies in Africa. Research questions for this study will be developed based on available literature on improving access to safe and effective medicines through collaborative medicines regulatory processes. The types of data collection techniques and tools such as surveys and questionnaires will be validated through literature search available in the public domain. To decide on which review to consider, a comparison of both systematic and narrative literature reviews will be carried out. Jahan et al (2016), have defined a systematic review as "A review of the evidence on a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant primary research, and to extract and analyse data from the studies that are included in the review". It is seen as a filter of the available information on a particular study as it analyses the information thereby improving the quality of evidence. With this type of review, the assessment is not biased while a narrative review or unsystematic review will often involve search of published sources selected by the authors which can introduce bias (Jahan et al, 2016).

Selected type of Literature review

This research is still a very new field with few available peer reviewed publications. Therefore, only the narrative literature review can be suitable and will be utilised for this study. Available literature for this study will be grouped into the following themes: national medicines regulatory systems in African countries; regional medicines regulatory harmonization initiatives in Africa; and the African Medicines Agency (AMA), which will then be subjected to narrative literature review. The outcomes from the narrative review will lead to the development of chapter one of this study, namely the General Introduction.

Search strategy

The following key words will be used to search bibliographic databases; medicines regulation in Africa, NRAs, AMRH, medicines regulatory harmonization, Regional Economic Communities (RECs), EAC-MRH joint assessment initiative, collaborative work sharing initiatives in medicines regulation, regulatory review processes, review models, good review practices and reliance. Numerous search engines such as PubMed, Google Scholar, SCOPUS, textbooks and open access theses will be used to perform the literature review and only articles written in English will be selected.

To ensure that relevant resources are found over the web, structured words to be used for the search engines will be developed as illustrated below:

- Inclusion criteria: This will be (1) all articles linked to specific tools or questionnaire on the medicine's regulation in Africa; (2) articles on medicines regulatory review processes and practices; (3) assessment of regulatory performance of work sharing/collaborative medicines regulatory initiatives; (4) Medicine regulation in East African countries; (5) The EAC-MRH programme; (6) The AMRH Initiative; (7) The AMA (8) Reliance mechanisms.
- Exclusion criteria: This will be (1) grey literature; (2) unpublished conference abstracts; (3) unofficial reports; and (4) any tools or studies that are not related to medicines regulation.

Questionnaires, semi-structured interviews and focus groups

Investigations using subjective techniques can be defined as a method of gathering data on a particular area of interest from a defined population using structured or semi-structured processes. Such investigations are meant to produce reliable data and results for a set of pre-defined and relevant objectives. It is these answers that will give objective responses to the research questions. (De Leeuw, 2005). There are different types of methods for collecting data for such investigations including; online platforms; mail-delivered questionnaires; in-person, virtual or telephone interviews using an interview checklist; telephone interviewer-administered questionnaires; and focus groups.. The researcher needs to have a critical evaluation of such methods before choosing the most appropriate one for their studies (Indeed Editorial Team, 2022). For the purpose of this research project, the following three methods will be employed to collect data from the representatives NRAs, and the generic and ethical pharmaceutical companies.

Questionnaires

A questionnaire is a tool with a series of standardized multidimensional questions which could be closed or open-ended used by researchers to collect information from the study sample. Researchers then draw results and make conclusions from the responses (Thurstone et al, 1929). There are several ways in which questionnaires can be administered; in person, over the phone, via mail, or online (De Leeuw, 2005). Self-administered questionnaires will be used for this study and will be shared with participants electronically. This is an efficient strategy to manage the resources for this study which are minimal, as respondents will be situated in different African countries. Also, using this method, a large sample of respondents can be recruited, and data can be collected simultaneously (Tariro, 2022). Another advantage of self-administered questionnaires is the possibility of ensuring anonymity of the respondent, if desired, therefore leading to more truthful and valid responses. The questionnaire can also be completed at a time convenient to a respondent. However, the risk with using this method is the low-response rate with no opportunity to clarify respondents' questions at the time of completion. Also, some information may be left out in cases where the questionnaire items have limited choices. Over the years, there has been a decrease in the response rate to questionnaires due to the large number being received (De Leeuw, 2005)

Questionnaire development

This research project will be using three questionnaires for data collection. One of these, the OPERA, is a validated established questionnaire which has track record for its use in such context (McAuslane et al., 2009) (Table 2.2).

Study 1 and study 2 will use the OPERA questionnaire (See Appendix 3) that was developed initially to assess the regulatory review process in emerging markets and how these processes affect patient access to safe and effective medicines (McAuslane et al., 2009). Before administering this questionnaire, a critical review will be carried out to ensure that the questionnaire will obtain responses to support the objectives of these two studies. The questionnaire will be shared with all the representatives of the NRAs in the countries in EAC. The aim of the questionnaire will be to evaluate the structure, organisation and resources of the NRAs, identify the types of review model(s) and key milestones in the review process for the scientific assessment of medicines in these countries, then examine the activities that contribute to Good Review Practices (GRevP) and quality decision-making processes. After the data has been collected, it will be analysed and the results compiled as individual country reports. These

reports will then be validated by the NRAs who completed the questionnaire after which a comparison will be made of the member countries of the EAC.

The other two questionnaires will be developed and validated specifically as part of this research project to rate the process effectiveness and efficiency (PEER) of the EAC-MRH initiative from both the regulatory agencies' perspective as well as that of the pharmaceutical industry (PEER-IND). The fully developed PEER and PEER-IND will be implemented for data collection in Study 3 and 4, respectively.

Applicability, practicality and Content validity

The OPERA questionnaire will be reviewed to ensure that it will be applicable to meet the objectives of study before its administration to the seven EAC national regulatory authorities. To examine the applicability, practicality, language clarity, ease of response accuracy, and the relevance of the questions for measuring theoretical construct, the PEER and PEER-IND questionnaires, will be piloted to 20% of the participants for each of the two groups (NRAs and pharmaceutical industry). The questionnaires will then be reviewed using results from the pilot study and then the final version will be produced. The following measurement properties of the newly developed questionnaires will be ensured prior to their implementation.

Applicability – is ensuring that the questionnaire items are relevant to the target population and useful for addressing the study objectives. It also assures that the outcome measured is of value to the intended end users and the questionnaire coverage is comprehensive in terms of positives as well as the challenges and provide plausible answer to the research question. This is also known as usability. Usability is "the extent to which a tool is objective, easy to administer and cost effective" (Streiner, Norman and Cairney, 2015).

Practicality - simply means that the findings from the research should be useful especially to the beneficiaries of the research. It is important for researchers to develop a checklist to assess the practicality of the methodological plan for the research (O'Leary, 2023). Study questionnaires should pose minimum burden on both the researchers as well as the respondents and the items should be easy to understand and straightforward to respond.

Reliability – is determining that the questionnaire/instrument is measuring something in a reproducible and consistent manner, minimising random error. One approach for assessing

reliability of a questionnaire/instrument would be to examine the agreement between two observers (Streiner, Norman and Cairney, 2015).

Content validity – is to determine if the questionnaire/instrument measuring what we think it is. The validity has to be determined for two reasons: 1) to establish the nature of what is being measured; and 2) to establish the relationship of that variable to its purported cause. As for the *content validity*, the questionnaire/instrument must be examined to make sure the content complies with what has to be measured. Such process determines whether the focus and the emphasis of individual questionnaire/instrument item is right for the concept being measured and is "fit for purpose" (Roebianto et al 2023). Cognitive debriefing interview has to be carried out as part of determining content validity in order to establish the relevance of the items to the target population and the concept being measured. Such process is usually carried out following completion of the newly developed questionnaire/instrument by the test cohort.

Interviewer-administered questionnaire

An interviewer-administered technique is administering of a questionnaire by an interviewer. It involves direct interaction between the interviewer and the interviewee. This can be either a physical meeting, over the phone, and/or online teleconference. The presence of the interviewer and a better understanding of the questions by the respondents can help both to increase the quality and response rate. It must made clear that the role of the interviewer in such mode of administration is to deliver the study questionnaire/instrument to the study participants, provide verbal instruction for completion and be present to clarify questions from the participants without influencing their responses. In this situation the interviewer has a chance to persuade a reluctant participant by providing additional verbal explanation in a neutral manner. The questions are pre-determined and can be open-ended or a checklist and other questions can be asked as the interviewer assisted administration of the questionnaire is proceeding (De Leeuw, 2005). The disadvantage of this type of technique is that the physical presence could result in the interviewer influencing the respondents' responses. It can also be costly and time consuming as it might entail one person travelling to meet the respondents, thereby limiting the number of contacts (Tariro, 2022).

Semi-structured interview

In this research, semi-structured online interviews will be carried out with the respondents following their completion of the self-administered questionnaires. The respondents will be

invited to have a conversation via the zoom online platform to obtain clarity on areas in the self-administered questionnaire that were not fully understood as well as providing additional information for each of the questionnaire items. This will also be an opportunity to complete some missing data.

Focus Group Discussions

This is another way of conducting in person interviews where the researcher will gather a small group of people to discuss specific questions. The researcher or the moderator of the discussion then ask questions and guide the discussions. Participants in the discussion are expected to interact with one another as they respond to the questions/issues being discussed (Indeed Editorial Team, 2022).

A summary of the selected data collection techniques

Table 2.2 below shows a summary of the selected data collection techniques for this research based on the research objectives.

Table 2.2: Summary of the planned data collection techniques.

Data collection technique	**Research Objectives**	**Thesis Chapter**
Narrative literature review	General Introduction Review of the EAC-MRH Initiative Review of the new regulatory ecosystem in Africa in the AMA era	Chapter 1
Part narrative literature reviews and part self-administered questionnaire	**Comparison of regional harmonization initiatives in Africa** Comparison of three regional medicines regulatory harmonisation initiatives in Africa (EAC-MRH, ZaZiBona and WA-MRH Initiatives)	Chapter 7 (Study 5)
Self-administered questionnaires	**Comparison of good review practices** Evaluation and comparison of the good review practices of countries participating in the EAC joint assessment (Kenya, Uganda, Rwanda, Burundi, South Sudan, Tanzania and Zanzibar)	Chapter 3 **(Study 1)**
	Comparison of regulatory review processes Evaluation and comparison of the Review Models and Approval Timelines of Agencies participating in the East African Medicine Regulatory Harmonisation Initiative (Kenya, Uganda, Rwanda, Burundi, South Sudan, Tanzania and Zanzibar)	Chapter 4 **(Study 2)**
	Regulatory Authorities evaluation of the effectiveness and efficiency of the EAC-MRH Initiative	Chapter 5 **(Study 3)**
	Pharmaceutical industry evaluation of the effectiveness and efficiency of the EAC-MRH Initiative	Chapter 6 **(Study 4)**
Semi-structured interviews	**Regulatory Authorities evaluation of the effectiveness and efficiency of the EAC-MRH Initiative**	Chapter 5 **(Study 3)**

RESEARCH FLOW

The research project for this PhD will begin with a narrative literature review (Appendix 1), focusing on critical analysis and overview of the EAC region regulatory environment. The first questionnaire (Appendix 2) will be reviewed and used to evaluate the regulatory review process for all products (Generics, NCEs, biological/biosimilars) in Kenya, Uganda, Rwanda, Burundi, South Sudan, Tanzania and Zanzibar. Two studies will emanate from this questionnaire; an evaluation and comparison of the good review practices of countries participating in the EAC joint assessment (Appendix 3). Through consideration of key milestones, timelines, and scientific review models, the data collected from these NRAs will be used to compare regulatory review processes and timelines amongst the countries in the region (Appendix 4). This will be followed by the development of a questionnaire and semi-structured interviews which will be used to evaluate the effectiveness and efficiency of EAC-MRH initiative from the regulatory authorities' perspectives (Appendix 5). A second questionnaire will then be developed to evaluate the effectiveness and efficiency of EAC-MRH initiative from pharmaceutical industry's perspectives (Appendix 6). The vision is that the analysis of data from these five studies and from chapter 7 where the three regional regulatory harmonization initiatives will be compared will lead to the recommendations for a proposed improved model for the EAC-MRH initiative (Chapter 8) and subsequently an improved patient access to medicines in the AMA era. The entirety of this PhD research project is captured in Figure 2.2.

Data Processing And Analysis

The qualitative and quantitative method will be used to process and analyze the data generated from this research. Following data collection, it will be necessary to initially identify only data that is needed for the studies. it will be cleaned to identify errors and gaps. Preliminary analysis of the exploratory data will be conducted to understand the characters, distribution and relationships of the data. The data will then be cleaned before analysis and interpretation of results. Since the studies planned for this research project are hypothesis generating, descriptive statistics will be used to analyse the quantitative data. Content analysis will be employed to analyse the qualitative data. The content analysis of the qualitative data will be carried out using a conventional approach, that is inductive coding based on the data, from which a set of cohesive themes will be generated.

An initial brainstorming will be conducted to examine the content of the data collected and identify initial concepts across the different forms of data collected. Data in the form of key phrases, statements, lists, will be independently extracted from the questionnaires and transcribed texts. A thematic analysis will be undertaken to familiarise with the different forms of data and add initial codes. Constant comparison across the different forms of data will inform an initial thematic framework to enable consistent coding of the data. If themes will be identified from the data that did not fit the initial coding framework, a new code will be established to involve the theme in the analysis.

The researcher will be working independently to identify themes, but then meet with the supervisors to discuss the themes and establish consensus. All themes, particularly where consensus could not be achieved, will be further discussed and agreed with the supervisors. This will enable analysis codes to be modified as new ideas will be developed. The researcher and the supervisors then comment on the proposed themes and supporting evidence. Reliability will therefore be established through discussion, and findings will be based on their agreement.

Microsoft Excel will be employed for collating, organising, analysing and presenting the results using tables and graphs (Figure 2.3).

ETHICAL APPROVAL

The research was approved by the Health, Science, Engineering and Technology ECDA, University of Hertfordshire, United Kingdom [Reference Protocol number LMS/PGR/UH/04988].

Figure 2.2 Research flow diagram

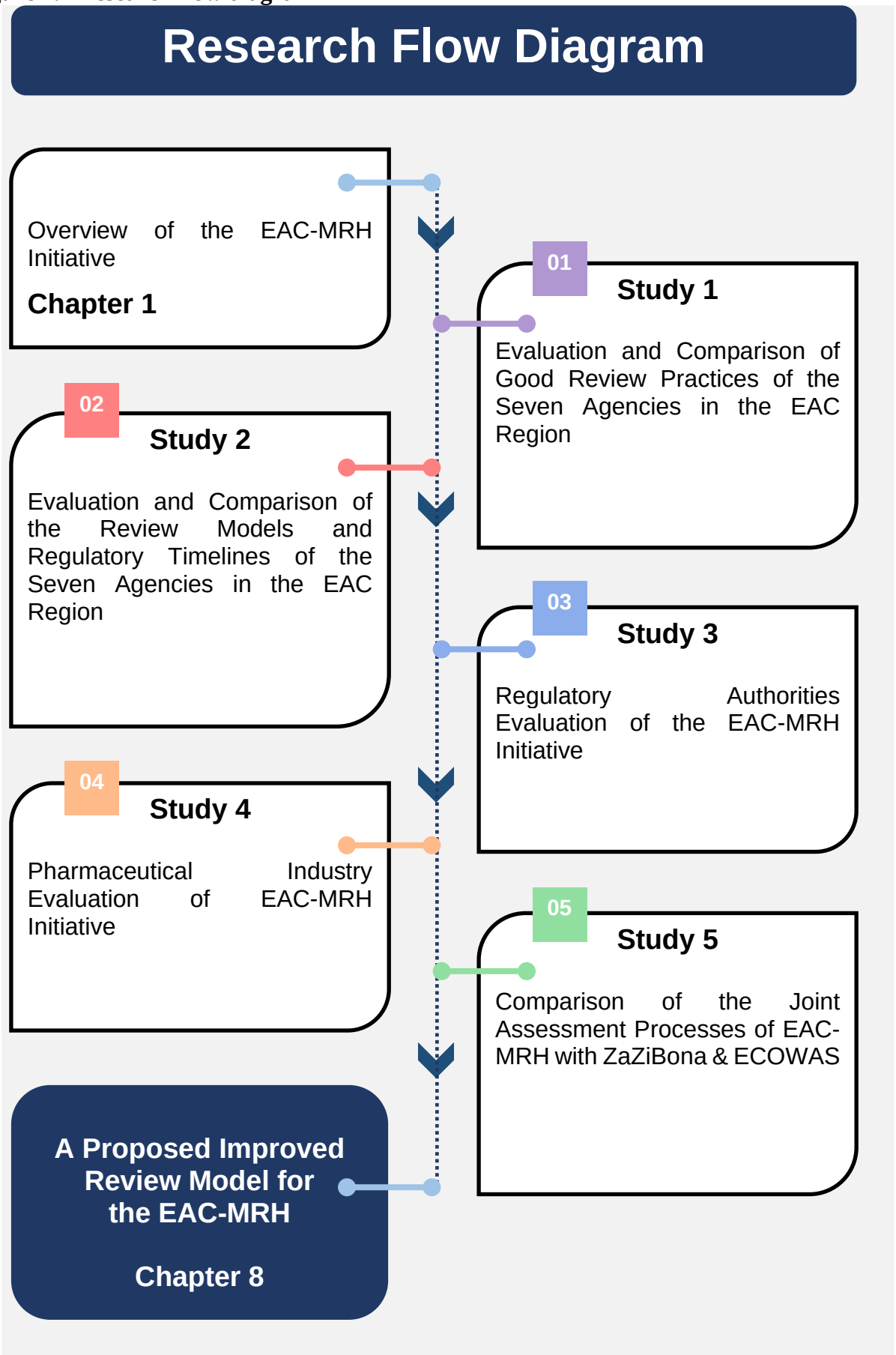
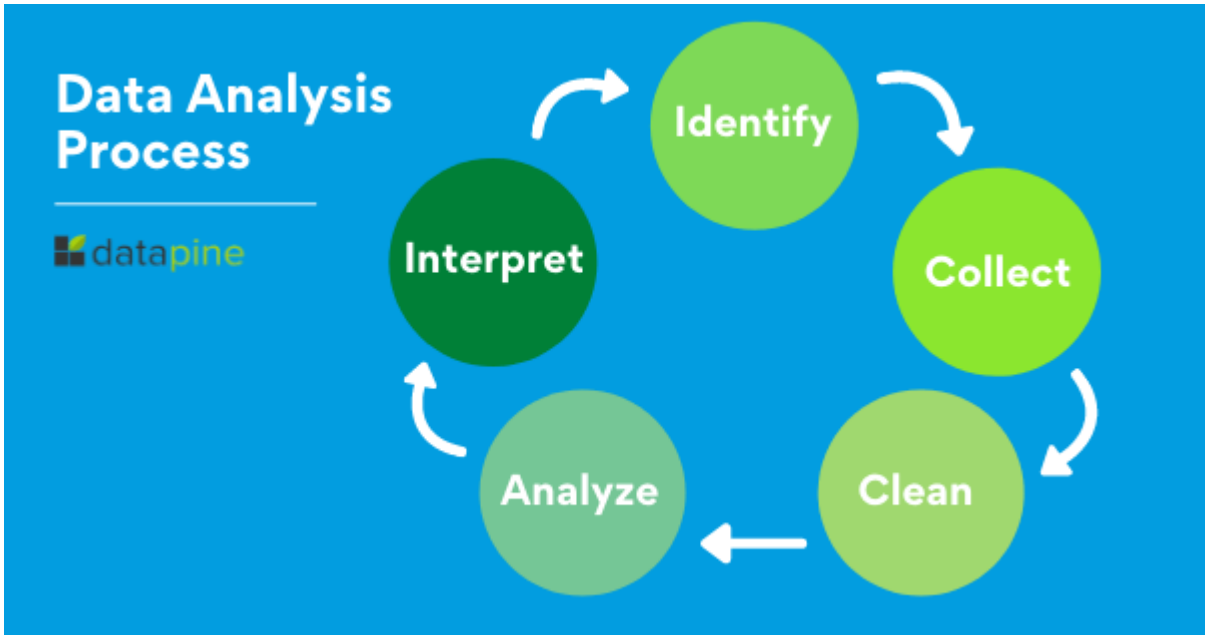


Figure 2.3 Data Analysis Process



Source: Calzon, 2023

SUMMARY

- This second chapter presents the rationale and purpose for conducting this research. It has also outlined the appropriate methodological framework for this research project.
- The study approach selected for this research is a combination of exploratory, descriptive, explanatory and evaluative methods.
- The research methodology for this project is a combination of qualitative and quantitative research methods.
- For the time horizon, a cross-sectional and retrospective study approach will be used for the research.
- The whole of the sampling frame is recruited into this study, that is senior officers heading the respective medicines registration departments of the individual authorities of the EAC-MRH member countries.
- A mixed quantitative and qualitative data collection and analysis technique are considered for this study –.
- The narrative literature review using numerous search engines was selected for this research project as well as preparation of Chapter 1 of this thesis, General Introduction.
- The selected data collection techniques for studies planned for this research project are questionnaires, semi-structured interviews and focus groups.

CHAPTER 3

EVALUATION OF THE GOOD REVIEW PRACTICES OF COUNTRIES PARTICIPATING IN THE WORK SHARING INITIATIVE

INTRODUCTION

The East African Community (EAC) is made up of seven countries: the Republics of Kenya, Uganda, Rwanda, Burundi, South Sudan, the Democratic Republic of Congo (DRC) and the United Republic of Tanzania. The DRC was recently admitted in 2022 after this study had been conducted. This intergovernmental organisation with a population of 303,397,152 has its headquarters in Arusha, Tanzania. The countries in this region have common medicines regulatory challenges such as differences in countries' laws and regulations, inadequate capacity with the National Medicines Regulatory Authorities (NRAs) of the region (Kamwanja, 2010 and Mashingia et al 2020). To address these challenges, the EAC Secretariat in collaboration with the EAC NRAs established the East Africa Medicine Harmonisation Project (EAC-MRH) in 2012 as the regional coordinating body of the AMRH Initiative. This was part of the implementation of one of the provisions of the EAC Treaty, Chapter 21, Article 118 on regional harmonisation in health (EAC Compendium, 2014).

The East African Community (EAC) Medicines Regulatory Harmonisation (EAC-MRH) programme was established to address the medicines regulatory challenges faced by the regulatory authorities of the region. Work sharing through joint assessments and inspections was adopted as an effective way to manage the limited resources and capacity while ensuring patients' timely access to medical products. However, the capacity and review practices of these agencies are also a key determinant of the success of the joint work. Faster registration of medicines even after a regional recommendation has been made, depends on the decision-making processes of the National Regulatory Authorities (NRAs). This study is therefore aimed to evaluate Good Review Practices (GReVP) in the agencies participating in the East African Medicine Regulatory Harmonisation Initiative.

Operational aspects of EAC-MRH

The East African Community (EAC-MRH) is one of the five regional medicines regulatory harmonisation programmes in Africa. There are seven national medicines regulatory authorities (NRAs) of the region participating in the EAC-MRH initiative. These countries share a common history, market, language, culture, and already had a treaty that called for these countries to harmonise. The aim of the programme since its inception was to reduce registration timelines of medical products through joint reviews and joint inspections with an overall goal to enhance access to safe, efficacious and quality medicines by patients in the region. Through harmonisation and work sharing for about ten years, 25 joint assessments have been conducted

with 202 products reviewed and 107 recommended for registration by the EAC Partner States (Ngum et al, 2023). However, due to the long bureaucratic process for the review and approval of the official notification letters to applicants, the median time for the communication of approval to the applicant following the scientific assessment generally exceeded the EAC target of 30 calendar days (Mashingia et al, 2023). Also, one of the key challenges faced by the work sharing initiative is the delay in granting marketing authorisation (MA) by the NRAs. The NRAs have varying timelines for products to be registered at a national level after a regional recommendation is made (Ngum et al, 2023). According to Mashingia et al (2023), the EAC target time for granting the MA of 116 calendar days was far exceeded in 2023 by all five authorities. The median times for granting MA by Burundi (ABREMA), Kenya (PPB), Rwanda FDA, Uganda (NDA), and Tanzania (TMDA) were 965, 683, 649, 582, and 515 calendar days, respectively. Several reasons have caused the long median times to grant the MA by the EAC NRAs; long administrative procedures, such as NRA requirements for product applications to be considered first by the scientific committee before a certificate of MA could be issued; delays by applicants in paying fees for registration after filing for MA in NRAs; NRAs in the region are operating at different maturity levels with limited capacities and capabilities to conduct timely scientific reviews with applicants expected to pay varying amounts for fees in the different NRAs (Table 3.1).

STUDY OBJECTIVES

This study is therefore aimed to evaluate Good Review Practices (GReVP) in the agencies participating in the East African Medicine Regulatory Harmonisation Initiative and map strategies for moving forward as they are going through the process of alignment for the operationalisation of the African Medicines Agency (AMA). This is the first in a two-part series and the next chapter will focus on the review models and timelines of these agencies.

METHODS

Study Participants

The study participants included Senior Programme Officers heading the Medicines registration divisions in the seven NRAs; Pharmacy and Poisons Board-PPB, Kenya; National Drug Authority-NDA, Uganda; The Tanzania Medical Devices Authority (TMDA); Zanzibar Food and Drugs Authority (ZFDA) Tanzania; Drug and Food Control Authority –DFCA South Sudan; Burundi Food and Medicines Regulatory Authority (ABREMA) and the Rwanda Food and Drugs Authority**.**

Data Collection

A validated questionnaire, Optimising Efficiency in Regulatory Agencies (OPERA) describing the organisation structures, regulatory review systems for market authorisation of new active substances (NAS's) and generics including their overall timelines from the date of submission of the application to when it is approved, good review practices (GReVP) and quality decision making practices, was completed by each of the agencies in 2022. The questionnaire was composed of six different parts: *Part 1* - Organisation of the agencies with focus on its structure and resources; *Part 2* – types of review models used by the agencies for scientific assessment of medicines; *Part 3* - key milestones in the review process with focus on the process map and milestones; *Part 4* – good review practices (GReVP) and how the agencies build quality into their regulatory processes; *Part 5* - quality of the decision-making processes based on whether the agencies have good measures in place to guide decision making; and *Part 6* – was based on concluding observations that relate to the strengths and challenges for the agencies to carry out its mandate (Appendix 3).

RESULTS

For the purpose of clarity, the results of this first study of the series will be presented in four parts: Part 1- Organisation of the regulatory authorities; Part II - Key Milestones in the review process; Part III - Good Review Practices; Part IV - Quality Decision-Making Practices.

Part 1: Organisation of the Regulatory Authorities

The population and size of the regulatory agency of the six countries in the region vary (Table 3.1). The top two countries with the largest population are Tanzania (65.4 million) and Kenya (54.9 million). Four countries (Kenya, Rwanda, Burundi, Zanzibar), have semi-autonomous agencies and operate within the administrative structure of their Health Ministries, while South Sudan, Uganda and Tanzania have autonomous agencies and are independent from their Ministries of Health. Six of the agencies regulate medicinal products, medical devices, and in vitro diagnostics for human and veterinary use and only the Burundian authority regulates medicines for human use and food and not veterinary use.

Most of the staff in the seven agencies are pharmacists; Kenya had the highest proportion of reviewers to total agency staff (16%) followed by Tanzania (13%), Burundi (12.5%), Uganda (11%), South Sudan (10%), Rwanda (8%), Zanzibar (8%). Only Tanzania indicated they used external experts for review of applications for marketing authorisation (Table 3.1).

If all applications received in 2022 were reviewed, then the number of applications reviewed per reviewer in each of the agencies would be 44 applications by Rwanda FDA, 36 in Kenya PPB, 26 by Uganda, 23 in Burundi (ABREMA), 19 in Tanzania (TMDA) 1 by Zanzibar, and 0 by South Sudan (DFCA). However, all the six agencies apart from South Sudan who does not receive, or review applications, indicated they had backlogs. Therefore, not all the applications received for that year were reviewed within the same period.

Table 3.1: Size of Agencies

Measure	BURUNDI	KENYA	RWANDA	SOUTH SUDAN	TANZANIA	UGANDA	ZANZIBAR
Population (millions)	13.1	54.9	13.2	11.3	65.4	45.7	1.7
Agency staff	32	170	188	42	336	292	150
Number of internal reviewers	4	28	15	4	45	33	12
Reviewers in Agency staff	12,5	16%	8%	10%	13%	11%	8%
Total applications received	70	997	659	0	858	861	10
Number of applications per reviewer	23	36	44	0	19	26	1

Source of Funding

The Burundi and South Sudan agencies were fully funded by their governments. The source of funding for Kenya and Uganda agency was reported to be entirely from fees, while Rwanda, Tanzania and Zanzibar were partially funded from different sources. For Rwanda 22% came from the government, 76% from fees and 2% donations from partners. For Tanzania, 11.7% government; 76.3% fees; 0.6% development partners and 11.4% balance from previous budget. For Zanzibar, Government provides 49.6%, Fees 41.6% and Donors 8.8%. The fees charged by each agency varied between $500, $1000 to $2000 based on the different kinds of application categories received (New chemical Substances, biologicals, and generics). Kenya charged the lowest fees ($500) for local manufacturers for all categories, while Tanzania charged the highest fees ($3500) for review of biologicals. Burundi and South Sudan agencies do not charge fees for applications for marketing as they are fully funded by government. The Burundi agency however charges fees for some activities such as registration and importation

and these fees are put into the national bank and not in the Agency bank account. Each year the Burundi government then gives the Agency a fixed budget for operating costs. (Table 3.2). Generally, agencies that fully depend on the government as their main source of funding charge less fees as compared to agencies that are fully reliant on fees.

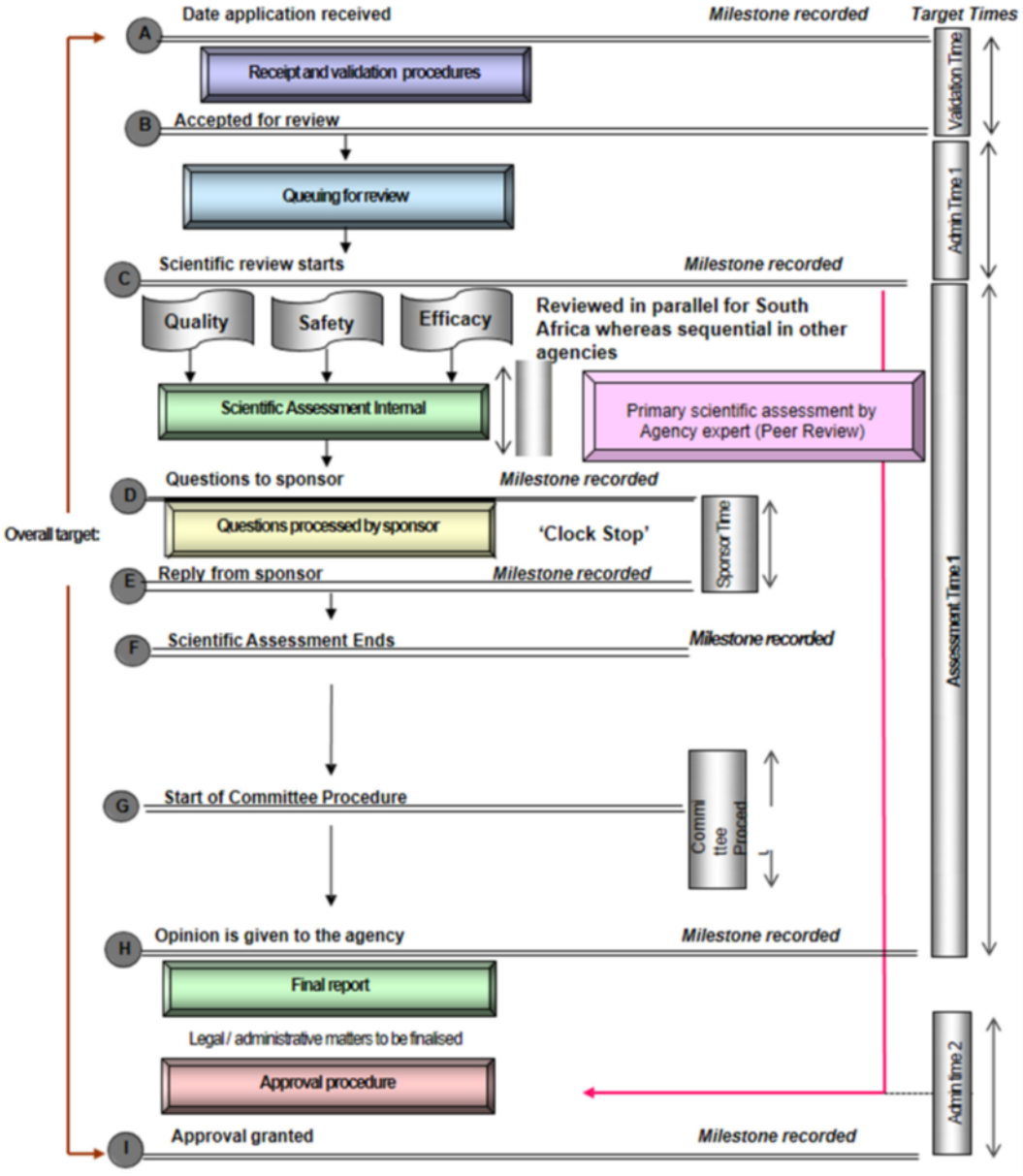
Table 3.2: Comparison of the fees charged (USD) and source of funding in 2023

Measure	BURUNDI	KENYA	RWANDA	SOUTH SUDAN	TANZANIA	UGANDA	ZANZIBAR
Source of funding	100% Government	100% Fees	Partially funded from different sources 22% Government 76% Fees 2% Donations from partners	100% Government	Partially funded from different sources (11.7% Government; 76.3% fees; 0.6% development partners; 11.4% balance from previous budget	100% Fees	Partially funded from different sources: % Government: 49.6% % Fees: 41.6% % Other (Donors): 8.8%
Total Annual Budget (USD)	400BiF 600.000.000 BIF	13,796,120	9,155,400	8 million SSP (2019-2020)	19,123,740	603,554	US$826,483 (2023)
Fees for review of a new chemical entity (USD)	N/A	1000 international 500 Local		N/A	2000	2000	N/A
Fees for review of biologicals (USD)	N/A	1000 international 500 Local	1250	N/A	3500	2000	2000
Fees for review of generics (USD)	N/A	1000 international 500 Local	1250	N/A	2000	2000	1000

Part II: Key Milestones in the review process

Figure 3.1 (Adopted from Sithole et al 2021) shows a standardised review process map being implemented in well-resourced regulatory systems with key milestones being recorded after each phase. This process map is a simplified version of the key steps taken during the review of a New Active Substance (NAS) and does not include rejections. The focus here is mostly on products that only go through one cycle of review although it usually will take more than one cycle for most applications to be reviewed and a recommendation made. South Sudan will not be part of the analysis in this section as DFCA is yet to engage in review activities as key points in the review procedure and timelines are not applicable or cannot be confirmed.

Figure 3.1 Standardised process map for the review and approval of medical products.



Receipt and validation procedure

All agencies indicated that when the application is received, they begin by checking for correctness; this is the validation procedure. If the application is incomplete, the applicant is notified. A time limit which varies across the agencies is given to the applicant to respond. If the timeline is not respected, then the application will be considered as withdrawn. Items checked at this stage may include the legal status of the applicant or local agent; the GMP status of the manufacturer; proof that correct fees have been paid; acceptable format which could include ICH, CTD or local requirement and correct sections of scientific data. It is at this point where the agencies decide the kind of review pathway that will be conducted (full review, abridged or verification). Successful applications are then placed in the queue for scientific assessments.

Queue time

After completion of the validation process, queue time commences, and this is the time between validation and start of primary scientific assessment. All agencies recorded this milestone but implementing different queue times ranging from a few weeks in some agencies to about one year in others. Tanzania (2 to 8 weeks), Burundi, Rwanda (2 to 6 months), Zanzibar (60 to 180 days), Uganda (12 months), for Kenya (more than one year). Priority products are not included in the queuing system.

Primary Scientific Assessment

Milestone 3 is the start of the scientific assessment which was recorded by all the six agencies. Rwanda, Zanzibar, Burundi and Uganda use internal technical agency staff for scientific assessments while Tanzania and Kenya, use both internal and external experts for the primary scientific assessment and detailed assessment report, recommendations and clinical opinion respectively. Four of the agencies indicated that scientific data being reviewed in their agencies is categorized into quality, safety and efficacy except for Burundi and Uganda who do not separate quality, safety and efficacy which are reviewed in this sequence by these agencies.

Questions to Applicants

All six agencies indicated that no meetings can be held by sponsors with the agency staff to discuss any queries emanating from the assessment. Rather, the questions are consolidated into a single batch and sent to the sponsor. At this stage, the clock stops for Kenya, Burundi, Zanzibar and Tanzania as the applicant is given time to respond. The clock stop time varies

from agency to agency. However, Uganda and Rwanda do not stop the clock while questions are being answered by the applicant, hence this can explain the difference in response times.

Review by Experts Committees

Five of the agencies engage a committee of experts in the review process. These experts are consulted after the agency has reviewed and reported on the scientific data. Target timelines for the start and finish for the committee vary from one day (Tanzania), one month (Uganda) to three months (Burundi and Zanzibar). Kenya does not have a target timeline for the committee. The report from the committee is presented to the board in most of the agencies for review. In some of the agencies (Burundi, Rwanda) they are mandated to follow the committee's recommendations, but other agencies are not mandated to do so (Uganda, Kenya, Tanzania).

Authorisation Procedure

Three of the NRAs (Kenya, Zanzibar and Uganda) inform their sponsors of a positive scientific opinion before the authorisation is issued, while the other three NRAs (Burundi, Tanzania and Rwanda) do not.

Part III: Good Review Practices

Quality Measures

A comparison of the quality measures implemented by the seven regulatory authorities is illustrated in Table 3.3. all agencies apart of South Sudan implemented all the eight quality measures; good review practice system, internal quality policy, standard operating procedures for guidance of assessors, assessment templates, internal peer review, have dedicated quality departments, availability the scientific committees and participation in shared and joint reviews. South Sudan did not implement any of the measures possibly because they are not currently reviewing any products.

Transparency and communication

On assessing the implementation of nine best practices on transparency and communication (Table 3.4), all six agencies reported that they have in place official guidelines to assist industry and a list of approved products that allow for industry to track the progress of their applications via email and telephone. Three agencies did not provide post-approval feedback to applicants on the quality of the submitted dossiers. Only two agencies (Rwanda and Uganda) provided details of technical staff to contact during the review of applications and only one country

(Uganda) publishes the advisory committee meeting dates. Three agencies namely Kenya, Uganda and Tanzania reported that they do publish summary of assessment reports on which the approval was granted.

Table 3.3: Comparison of the quality measures implemented by the seven regulatory authorities.

Quality Measure	Regulatory Authority						
	BURUNDI	KENYA	RWANDA	SOUTH SUDAN	TANZANIA	UGANDA	ZANZIBAR
Good review practice system	✓	✓	✓	x	✓	✓	✓
Internal quality policy	✓	✓	✓	x	✓	✓	✓
Standard operating procedures for guidance of assessors	✓	✓	✓	x	✓	✓	✓
Assessment templates	✓	✓	✓	x	✓	✓	✓
Peer review (internal)	✓	✓	✓	x	✓	✓	
Dedicated quality department	✓	✓	✓	x	✓	✓	✓
Scientific Committee	✓	✓	✓	x	✓	✓	✓
Shared and joint reviews	✓	✓	✓	x	✓	✓	✓

x-not implemented.

✓ formally implemented.

Continuous improvement initiatives

Five areas (external and internal quality audits; internal tracking systems, reviews of assessors' and stakeholders' feedback), were assessed to determine continuous improvement initiatives in the six regulatory authorities (Table 3.5). Tanzania implemented all five initiatives, while Uganda Kenya and Zanzibar implemented four out of the five initiatives. Rwanda implemented three and Burundi implemented two out of five.

Table 3.4: Comparison of the transparency and communication parameters in the six agencies.

Quality Measure	Regulatory Authority						
	BURUNDI	**KENYA**	**RWANDA**	**SOUTH SUDAN**	**TANZANIA**	**UGANDA**	**ZANZIBAR**
Post-approval feedback to applicant on quality of submitted dossiers	✓	✓	x	x	x	✓	✓
Details of technical staff to contact	✓	x	✓	x	x	✓	x
Pre-submission scientific advice to industry	✓a	✓	✓	x	x	✓	x
Official guidelines to assist industry	✓	✓	✓	x	✓	✓	✓
Industry can track progress of applications	✓	✓	✓	x	✓	✓	✓
Publication of summary of grounds on which approval was granted	X	✓	x	x	x	✓	✓
Approval times	✓	✓	✓	x	✓	✓	✓
Advisory committee meeting dates	x	x	x	x	x	✓	x
Approval of products	✓	✓	✓	x	✓	✓	✓

x-not implemented

✓ formally implemented; ✓a informally implemented

Training and Education

The following measures were assessed that contribute to the development of staff and the efficiency of the regulatory review process, through training and education; training programme for assessors, international workshops, external courses, in-house courses, on the job training, external speakers invited to the authority, induction training, sponsorship of postgraduate degrees, placements and secondment in other regulatory authorities. All six countries implement most of such measures. However, Burundi, Kenya and Uganda did not have a policy in place to invite external speakers to the authority, Burundi and Rwanda did not sponsor postgraduate degrees; Uganda reported that they do not host international workshops

or conferences and along with Burundi and Rwanda do not make placements and secondments in other regulatory authorities.

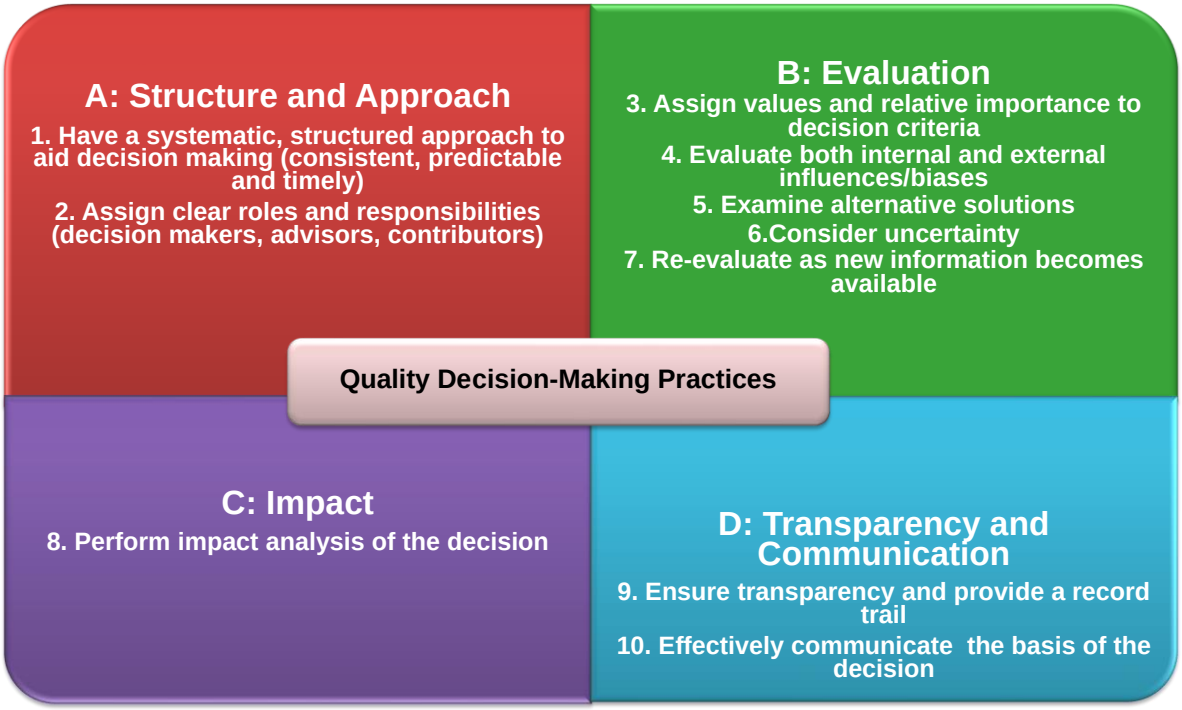
Table 3.5: Comparison of continuous improvement initiatives in the six regulatory authorities.

Quality Measure	Regulatory Authority						
	BURUNDI	KENYA	RWANDA	SOUTH SUDAN	TANZANIA	UGANDA	ZANZIBAR
External quality Audits	x	x	x	x	✓	x	x
Internal quality Audits	✓	✓	✓	x	✓	✓	✓
Internal tracking Systems	✓	✓	x	x	✓	✓	✓
Reviews of assessors' feedback	✓	✓	✓	x	✓	✓	✓
Reviews of stakeholders' feedback	✓	✓	✓	x	✓	✓	✓

Part IV: Quality Decision-Making Practices

Ten quality decision-making practices were used to determine whether these agencies have measures in place to ensure that quality decisions are made using the data submitted during the review of applications. These include: 1. Have a systematic structured approach to a decision-making, 2. Assigned clear roles and responsibilities, 3. Assign values and relative importance to decision criteria, 4. Evaluate both internal and external influences./ biases, 5. Examine alternative solutions, 6. Consider uncertainty, 7. Re-evaluate as new information becomes available., 8. The form impact analysis of the decision, 9. Ensure transparency and provide a record trail, 10. Effectively communicate the basis of the decision. Out of the ten quality decision-making practices, Kenya implemented four, Rwanda eight, Zanzibar three, Uganda five, Burundi eight and Tanzania implemented all the ten quality practices.

Figure 3.2 Quality Decision making practices (QoDos)



DISCUSSION

The aim of this study was to evaluate Good Review Practices (GReVP) in agencies participating in the East African Medicine Regulatory Harmonisation Initiative and map the strategies aligning with the African Medicines Agency. Comparing the similarities and differences of agencies in this region will assist them through information sharing to identify best practices in the process and documentation of the review procedures. It will also assess how these agencies build quality into their review processes. Ensuring standardisation, improvement in documentation, timeliness, predictability, consistency and high quality of reviews and review reports will entail efficient and effective GReVP in regulatory agencies (Reference). One of the key challenges faced by industry in applying for marketing authorisation has been the lack of detailed information (Ngum et al, 2022) on the regulatory procedures for applicants. This study which is similar to one conducted by Sithole et al, (2021) for the SADC region should raise awareness for the industry as well as applicants on the regulatory processes for each agency. This will enhance transparency and clarity on the

application process thereby leading to an increase in investments in medicines development and improved submission of applications to agencies in the region.

As a result of the participation of all the EAC agencies in the regional harmonisation initiative, they are now operating either as autonomous (3 agencies) or semi-autonomous agencies (4 agencies). This has therefore improved the regulatory review processes of these agencies. One of the key challenges for regulatory systems strengthening in most countries in Africa is the absence of an autonomous National Medicines Regulatory Authority (NRAs) mandated to regulate the market. In countries where regulatory functions are split among two or more agencies, there is usually duplication of effort, lapses in implementation, inconsistencies and spreading of limited resources too thinly. With autonomous agencies, efficiency and effectiveness can be ensured as this governance structure enables the agency to focus on regulation (Dube-Mwedzi1et al, 2020). The African Union Model Law on medical products regulation (AU Model Law) provides for the establishment of autonomous NMRAs for effective coordination and regulation of medical products in a country. However, article five of the AU Model Law recommends that agencies should be fully autonomous. This law was endorsed by the Heads of States and Governments in 2016 (Ncube et al, 2023) whose objective is to promote collaboration across countries and provide an enabling environment for the manufacturing, testing and scaling up of essential and priority medical products in Africa. Five out of the six countries in the region have comprehensive legal frameworks thereby providing a good foundation for effective regulation (Ndomondo-Sigonda et al, 2021).

Challenges of human resource constraints are faced by all the agencies as they all had backlogs during the period of the study. Even though one of the strengths of the EAC-MRH initiative has been building the capacity of assessors in the region (Ngum et al, 2022), there is still a significant gap in terms of numbers of assessors in these agencies as per the results of this study. Strengthening of the harmonisation initiative, operationalisation of the African Medicines Agency and reliance on well-resourced agencies by less resourced agencies are being proposed as some of the immediate interventions to address the challenge of limited resources (Ngum et al, 2022 and Shabani et al, 2022). However, the results of this study demonstrate that the NMRAs receiving the highest number of applications (Tanzania, Kenya, and Uganda) use both internal and external experts for the primary scientific assessment while the NRAs with less applications for review utilise only their internal technical agency staff for scientific assessments.

One of the major challenges observed in this study is the recording of the timelines for each milestones achieved. These all vary amongst the NRAs in the regions with most agencies not implementing a routine recording of timelines for key indicators such as timelines for validation, start of scientific assessment, response to questions to applicants, finalising scientific assessment and date of registration. This comparative study will act as a baseline and will assist the NRAs to reflect on their key performance indicators as they build on the continuous monitoring of performance. Assessing the current situation will be a guide for making informed decisions on how to improve regulatory performance (Sithole et al, 2021) as countries should learn from each other on how NRAs with similar resources conduct their reviews.

This study is also crucial for the EAC-MRH initiative especially as this relies on country processes to register medical products that have been recommended by the joint review process. The current observation is that countries delay implementing the recommendations from the regional process. It is therefore important for the EAC-MRH program to revise its process to limit dependency on the country processes which are already overwhelmed with the national workload. The understanding of country-specific requirements that follow an EAC-MRH positive opinion to address reasons for further delays in the approval process is key for the alignment to the African Medicines Agency (Ngum et al, 2022).

RECOMMENDATIONS

The following are the recommendations emanating from this study have been listed below in order of implementation priority.

1. **Measuring & Monitoring Timelines**. Agencies in the EAC-MRH initiative should implement systems that will enhance the measurement and monitoring of timelines for the key milestones of the registration process such as dates of submission, validation, start of scientific assessment, completion of scientific assessment and registration.
2. **Applicants Communication**. Clear registration processes should be documented and shared with the applicants as well as publishing timelines, assessment reports, and the summary basis of approval which will facilitate transparency and accountability.
3. **Quality Decision-Making Practices**. Although all the agencies indicated they are implementing the quality decision making practices, there is still a need for training and education in this area**.**

4. **Reliance.** The EAC-MRH should review and develop a roadmap for the implementation of reliance.
5. **Work-Sharing**. The EAC-MRH operating model should be reviewed to identify areas of improvement that will enable effectiveness and efficiency of the programme. The EAC-MRH should develop measures to mandate the registration of products at a national level following regional recommendation. This approach would ultimately lead to faster availability of medicines to patients as well as reducing demand on capacity.

CONCLUSIONS

For the African Medicines Agency to be successful and achieve its objectives, country regulatory processes need to be streamlined and differences in country requirements minimised. Like the EAC-MRH, the AMA will also depend on countries to implement the decisions recommended by this continental body. It is therefore crucial that the groundwork in the operationalisation of the AMA focuses on improving the review practices of the NRAs so as to minimise any delay in granting marketing authorisation to medical products. It is imperative for countries to implement good review practices in order to accelerate patients' access to safe, quality and effective medical products when the African Medicines Agency is established.

SUMMARY

- The aim of this study was to evaluate the Good Review Practices (GReVP) in the agencies participating in the EAC-MRH Initiative.
- A validated questionnaire (Optimising Efficiencies in Regulatory Agencies) was completed by each of the agencies in 2022/ 2023
- On governance, four of the countries have semi-autonomous agencies while three have autonomous agencies.
- On the source of funding, the Burundi and South Sudan agencies were fully funded by their governments, entirely from fees for Kenya and Uganda agencies, while Rwanda, Tanzania and Zanzibar were partially funded from different sources.
- All the six agencies apart from South Sudan who does not receive, or review applications had backlogs.
- The key milestones for standardized regulatory processes are implemented in all the agencies with some differences identified.
- Queue times are different ranging from a few weeks in some agencies to about one year in others.
- Three of the agencies use internal technical agency staff for scientific assessments while three use both internal and external experts for the primary scientific assessments.
- The clock stop time varies from agency to agency. Target timelines for the start and finish for the review committee vary from one day (Tanzania), one month (Uganda) to three months (Burundi). Kenya does not have a target timeline for the committee.
- All the agencies are implementing some best practices on quality measures, transparency and communication.
- Some have activities for transparency improvement but with minimal attention to training and education. Most of the agencies have some measures in place for quality decision-making practices.
- All NRAs except Burundi are implementing a quality policy while except for Uganda and Zanzibar all four NRAs have a dedicated quality department. All six NRAs participated in shared and joint reviews.
- Tanzania and Zanzibar implemented all five continuous improvement initiatives.
- For the AMA to be successful, country regulatory processes need to be streamlined and differences in country requirements minimized.

CHAPTER 4

EVALUATION AND COMPARISON OF THE REVIEW MODELS AND APPROVAL TIMELINES OF AGENCIES PARTICIPATING IN THE EAST AFRICAN MEDICINE REGULATORY HARMONISATION INITIATIVE

INTRODUCTION

One of the key functions of National Medicines Regulatory Authorities (NRAs) is the review of applications and registration of medical products submitted by pharmaceutical manufacturing companies. The NRAs are expected to have effective and efficient regulatory systems to ensure that the timely marketing authorisation is granted to safe, effective and good quality medical products. One of the objectives of establishing the EAC-MRH project was to build capacity of NRAs in the region through work sharing, training and twinning. Currently there is a strong advocacy on reliance especially as most of these agencies delay issuing marketing authorisation for medical products leading to a significant backlog.

Over several years, the process of medicines regulatory harmonisation has been embraced by many National Regulatory Authorities (NRAs) to improve public health through faster availability of safe, quality, and effective medical products to patients. This has enhanced the harmonisation of technical guidelines and work sharing leading to reduced costs to pharmaceutical companies as they prepare one single set of applications to submit to several countries. After ten years of implementing regulatory harmonisation by the EAC-NRAs, it is now imperative for these NRAs to rely on each other so as to minimise duplication of their use of limited resources. One of the major challenges in implementing reliance is the lack of clear registration processes in the NRAs and the delay in the approval of medical products.

Reliance

With the complexities that come with the granting of marketing authorisation for medical products, most regulatory authorities are now embracing the concept of reliance as a way of improving performance. It is now clear that no one agency can do it all especially with new advanced health technologies and emerging public health diseases plaquing the world. Facilitated regulatory pathways (FRPs) are regulatory pathways designed to speed the development, marketing authorization, and patient access to new drugs with a positive benefit–risk balance by providing alternatives to standard product development and regulatory review routes. It should be noted that it is possible for an FRP to not use reliance, for example if an NRA has a priority review pathway or an accelerated review pathway, it might move that application to the top of the pile and direct its resources towards evaluating that application quickly, without relying on prior assessments especially if that product is new and has not been registered anywhere in the world (Liberti et al, 2017 & FDA). The main objectives of the harmonisation initiative are to build trust amongst NRAs so that they can rely on each other's

decisions. According to the World Health Organisation (WHO) guidelines on good reliance practices, NRAs are encouraged to implement reliance to minimise duplication of effort especially given their limited resources. Countries with weak regulatory systems are called upon to rely on the WHO Listed Authorities (WLA). According to the CIRS 2022 R&D briefing 85, there has been an increase in the use of facilitated regulatory pathways even by well-resourced NRAs in the past five years for approval of new medicines to ensure patients' timely access to safe, quality and effective medical products. Therefore, Regulatory reliance and work sharing will help low- and middle-income countries to have access to innovative medicines in a timely manner (McAuslane et al, 2023).

WHO pre-qualification procedure

Launched in 2001, the WHO Pre-Qualification (WHO PQ) of Medicines Programme directs United Nations organizations about the quality of some selected medicines within the selected scope (the quality of medications for the treatment of infections with the human immunodeficiency virus, acquired immune deficiency syndrome (AIDS/HIV), malaria, and tuberculosis). The WHO Prequalification Team was established in 2013 when the program combined with the WHO Pre-Qualification of Diagnostics Programme and Vaccines. One of the roles of the team is assessing medicines, awarding prequalification, monitoring variations, periodical re-qualifications, reinspection of manufacturing sites and field quality surveys (Giralt et al, 2020).

The EAC NRAs, the EAC-MRH and the EMP-TC procedures recognize the WHO PQ as one of the reliance pathways. Products approved through the WHO PQ maybe eligible to the EMP-TC process for the Technical Committee to coordinate and conduct an assessment for Africa or targeted countries specific requirements (provided that the product meets the criteria of complexity and number of RECs and or number of countries targeted). This may range from a verfication assessment to only facilitating CRP. It should be noted that the WHO PQ scope is very narrow with only ATM products and some pediatric products.

As per requirements, applications that are WHO prequalified are not encouraged to be applied through EAC-MRH joint assessment route. This was agreed in order to save resources as enough work has been done by the WHO prequalification team already. As we know, most sub-Saharan countries face a challenge of fragmented legal frameworks, weak management structures and processes, and a severe lack of staff and resources this makes these regulators to operate with minimal capacities. The WHO prequalified applications are required to be channelled through national route as most work has been done by WHO therefore it will not

be necessary to review them through the worksharing forum. However, EAC-MRH has a guidance in place for the partner states in EAC to adhere to when they receive such applications.

TMDA on behalf of EAC coordinates all medicines applications applied for marketing authorization through the EAC route.

TMDA coordinates such applications applied through the national route in two aspects of handling;

1. Applications that are WHO prequalified medicinal Products and
2. Applications of Medicines approved by Stringent Regulatory Authority (SRA) submitted under Collaborative Registration Procedures (CRP).

Through the procedure, applicants do select the type of application by the time they apply in the TMDA RIMS system and express their interest by confirming presence of signed and dated WHO expression of interest form to register under CRP. During assessment of technical information TMDA focal point do communicate with WHO on accessing prequalification technical assessment report documents.

For SRA/WHO Listed Authority (WLA) approved products, the applicant may also share the redacted assessment reports provided by reference SRA/WLA through TMDA. This also accounts for using an abridged assessment that reduces the need to assess all the data. However as per abridged assessment, TMDA requires applicants to submit all data and information required for full review i.e. full CTD module. Evaluators may need to review the data in the dossier as required even when presented with unredacted reports. Normally all decisions regarding approval and final registration will be made by TMDA with consideration of multiple factors including GMP status of the site producing the prequalified product and the status of reference SRA/WLA.

Registering Medical Products in LMICs:

The main function of NRAs is to register medical products in their countries. This is also known as granting marketing authorisation or product licensing (Rago et al, 2008). Countries have different regulatory requirements for the registration of pharmaceutical products. Understanding the review models and approval timelines for the East African Community as an emerging market for pharmaceutical companies is critical (Shelke et al,2020) in fast tracking the registration process to provide the much-needed medical products to patients in a timely manner. There has been a general indication that for applicants interested in these markets that the NRAs should ensure that the application procedures are clear, that communication and

transparency is enhanced, with timelines for approval of products clearly outlined, with registration guidelines for countries in the same region being harmonised and registration processes being effective and efficient (Sithole et al, 2021; Ngum et al, 2022b). However, reviewers have also raised the challenge that the long review timelines experienced in the registration of medical products are sometimes caused by the delay in manufacturers' or applicants' response to queries. It is therefore important to understand that these requirements from the regulatory authorities on the review models used should inform the industry and other stakeholders on what to expect from the agencies. The first paper of this series focused on comparing the key milestones in the review process using a general model with a process map and milestones. It also examined how these agencies build quality into the review by analysing their good review practices. Lastly this paper has examined how quality is built into the decision-making practices of the EAC NRAs as it reviews whether there are measures in place to guide good decisions.

The aim of this paper which is the second of this series is to compare the review models, target timelines and data requirements utilised in assessing applications for registration by countries participating in the EAC-MRH initiative so as to align and propose strategies for improvement.

METHODS

Study participants

The study participants included Senior Programme Officers from the Medicines registration divisions in the seven NRAs; Pharmacy and Poisons Board-PPB, Kenya; National Drug Authority-NDA, Uganda; The Tanzania Medical Devices Authority (TMDA); Zanzibar Food and Drugs Authority (ZFDA) Tanzania; Drug and Food Control Authority DFCA South Sudan; Burundi Food and Medicines Regulatory Authority (ABREMA) and Rwanda Food and Drugs Authority.

Data Collection

A validated questionnaire (Optimising Efficiencies in Regulatory Authorities: OpERA) describing the organisation structures, regulatory review systems for market authorisation of new active substances (NASs) and generics including their overall timelines from the date of submission of the application to when it is approved, good review practices (GrevP) and quality decision making practices, was completed by each of the agencies in 2022 and 2023. The questionnaire is composed of six different parts: Part 1 documents the organisation of the agency with the focus on its structure and resources; Part 2 covers the types of review models

used by the agency for the scientific assessment of medicines; Part 3, is based on key milestones in the review process with the focus on the process map and milestones; Part 4 relates to good review practices (GrevP) and how an agency builds quality into their regulatory processes; Part 5 focuses on the quality of the decision-making processes based on whether the agency have good measures in place to guide decision making, and Part 6 describes the challenges and opportunities available to the national regulatory agencies (Appendix 3).

Models of Regulatory Review

A Risk based approach to the review involves different review models which describe the ways in which agencies access the scientific data received from applicants during the assessment process. This can vary depending on whether the data is assessed in detail by the agency, or the agency relies on results of the assessment conducted elsewhere. The decision to choose which type of review model will also depend on the type of product and its status with other agencies.

The different steps in the review process do have a significant effect on the review timelines and subsequent market authorisation. There are three types of review models which NRAs can use namely;

The verification review (Type 1) which is used to minimise duplication by allowing a product that has been registered in a recognised agency to be marketed in the receiving country. The main responsibility of the receiving country is to verify that the product has indeed been registered elsewhere and is exactly the same product.

The abridged review (type 2) model also minimises the use of resources by not reviewing scientific data that has been assessed elsewhere but focuses on reviewing the product based on its local conditions which could be climate, infrastructure for distribution, benefit-risk assessment, and medical practice culture.

The full review (type 3A or 3B) is when the agency assesses the complete application including all the scientific data of quality, safety and efficacy, but requires that the product be previously reviewed by an agency and issued a Certificate of Pharmaceutical Product (CPP). Type 3B involves an independent assessment of a product's quality, preclinical and clinical safety and efficacy. This is carried out with applications that have not been reviewed elsewhere and requires more human resources and an improved infrastructure. Thus Type 3B does not use reliance (Sithole et al, 2021).

RESULTS

For the purpose of clarity, the results of this study will be presented in three parts: Part 1: Metrics of applications received and registered; Part 2: Review models, extent of scientific assessment and data requirements and Part 3: targets of key milestones in the review process.

Part 1: Metrics on NASs, generics, and WHO Prequalified Generics

All seven countries completed the OpERA Questionnaire. However, South Sudan did not report any data since they had not received any application for the specified study period. Kenya received 55 applications for NASs in 2020 and approved 18 and received 53 applications in 2021 out of which 47 were approved. In 2022 Rwanda received 409 applications for NAS and approved 160 and in 2023 received 398 applications and approved 60. (Table 4.1).

All the six NRAs received applications for generics with Tanzania approving the highest number of applications (499) for 2020 and (503) for 2021. It is interesting to note that the number of generics approved by Tanzania dropped in 2022 to 359. Kenya had received more applications (692) in the same year (2020), but only granted marketing authorisation for 81 products. Burundi in 2020 received 157 applications and approved 110 but in 2023 approved 57 with 342 applications received. In 2021, Kenya received 909 applications and only approved 368 while Uganda received 849 and approved 405. Burundi on the other hand did not approve any product in 2021 even though they received 68 applications. Uganda received the highest number (849) of applications in the region in 2021 and was able to register 405 generic products during the year. Tanzania in 2021 received 704 applications and registered 503 while Zanzibar received 10 applications in the same year but only approved two in 2022 (Figure 4.1).

Kenya and Rwanda saw a slight increase in WHO pre-qualified generics approved in 2021 while Burundi and Zanzibar did not receive WHO pre-qualified applications. Tanzania in 2021 received 15 WHO pre-qualified applications and approved 13. For Uganda there has been a decline in the number of WHO pre-qualified applications from 2021 to 2023 (Table 4.1).

Mean Approval Times

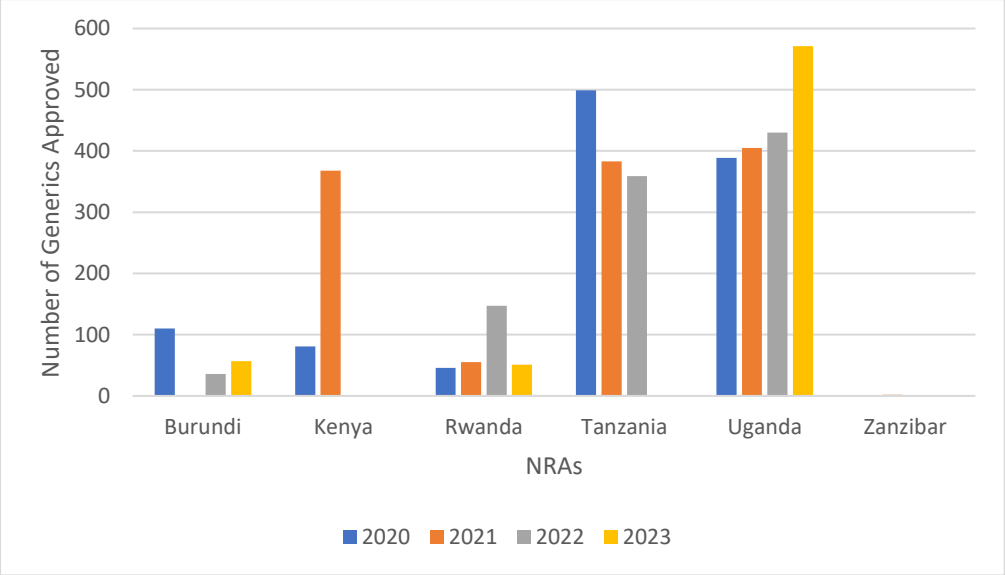
While Kenya received a number of applications for NASs, they approved 18 applications in 2020 and 47 applications in 2021 (Table 4.1), but they did not indicate the mean approval times for a full review of NAS applications (Table 4.2). For full review of generics, Tanzania saw a decline on the mean approval times for the three years consecutively (202 days in 2020, 93

days in 2021 and 61 days in 2022) to approve generics. Rwanda took (1035 days) in 2022 and declined to 735 days in 2023 while Kenya increased from 575 days in 2020 to 739 days in 2021 days by Kenya in 2021. Zanzibar also increased from 480 days in 2021 to 630days in 2022. The mean approval timelines for generics Uganda saw a slight decrease in 2022 (283 days) from 261 days in 2021. However, there was an increase in 2023 to 238 days. (Figure 4.2).

For WHO pre-qualified applications, Rwanda (484 days) and Kenya (341days) took a longer mean approval times using full review while the other countries took less than 100 days for the approval of generics (Table 4.2).

Using verification review type, an average of 90 days was used by Burundi and Zanzibar in 2022 for WHO pre-qualification. Zanzibar also reported taking a mean approval time of 78 days to review the EAC-MRH recommended applications. From 2020 to 2023, Uganda has less that 65 days as mean approval times for generics and WHO pre-qualified products. Kenya and Rwanda did not report the mean approval times for verification review type for NASs, Generics and WHO pre-qualified applications (Table 4.2).

Figure 4.1 Comparison of number of generics approved from 2020 to 2023.



For the abridged review type, Zanzibar spent 180 days in 2020 as mean approval times for generics. Burundi took 90days in 2022 for WHO pre-qualification while Tanzania took 14 days in 2021 and 13 days in 2022. In 2021, Rwanda took 484 days for approval of WHO pre-

qualification application. Kenya and Rwanda did not submit information on mean approval times when using the abridged review type (Table 4.2).

Figure 4.2 Comparison of mean approval times for generics using full review from 2020 to 2023

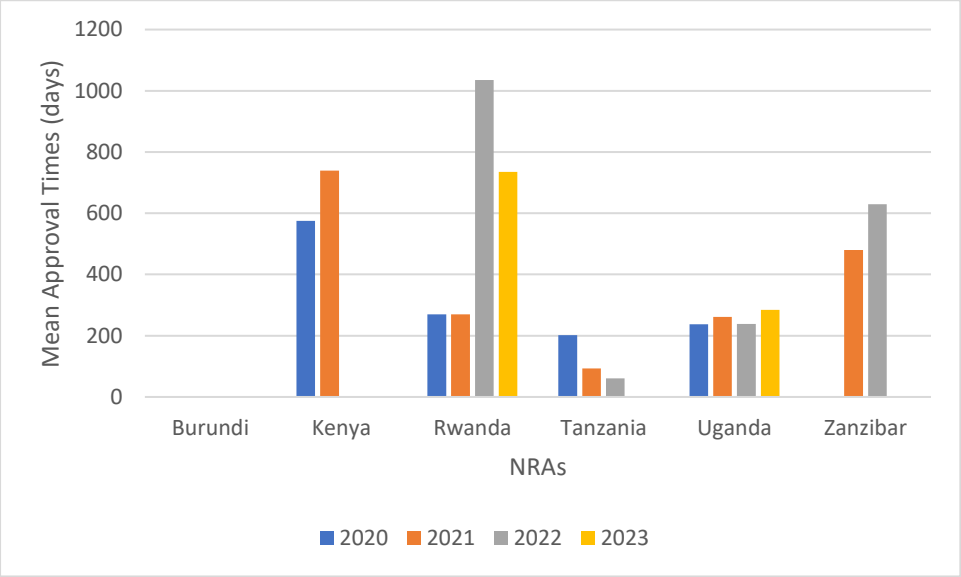


Table 4.1: Comparison of metrics for NASs, generics, and WHO prequalified generics (2020–2023).

Country	Burundi				Kenya				Rwanda				Tanzania				Uganda				Zanzibar			
Year	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023
NASs																								
Received	0	0	0	0	55	53			0	0	409	398	0	0	0	0	NS	NS	0	0	0	0	0	0
Approved	0	0	0	0	18	47			0	0	160	60	0	0	0	0	NS	NS	0	0	0	0	0	0
Generics																								
Received	157	68	80	342	692	909			533	615	390	379	631	975	1,079	764	508	849	804	905	8	10	14	22
Approved	110	0	36	57	81	368			46	55	147	51	499	383	359	51	389	405	430	571	1	2	0	0
WHO Pre-qualification																								
Received	0	2	0	1	10	35			16	18	7	3	7	22	16	14	10	12	7	6	1	0	0	0
Approved	0	0	4	1	10	20			0	11	7	0	7	14	13	12	10	12	7	3	1	0	0	0

NASs, new active substances; WHO, World Health Organization; N/S, Not specified

Part II: Review Models Used for Scientific Assessment

All of the six agencies carry out full and abridged reviews for scientific assessment.

Verification Review (Type 1)

Burundi, Tanzania and Zanzibar do not conduct verification reviews for generics. However, Burundi and Zanzibar do use verification review for WHO prequalification and EAC-MRH recommended applications. The reason for not implementing type 1 assessment by TMDA is that they do not implement mutual recognition policies yet. The agency offers special import permits based on its regulations. Kenya and Rwanda conduct verification reviews for selected applications like WHO pre-qualified products, and products approved by WHO Listed Authorities (WLA) and agencies who have valid agreements to share reports. For Uganda, this is for WHO collaborative registration procedure (CRP) and EAC-recommended products (Table 4.3).

Reference agencies used by the NRAs include WHO-prequalification programme agencies, ICH founding members and WLAs such as Swissmedic, mature European Union agencies, European Medicine Agency (EMA), United States Food and Drug Authority (US FDA), Health Canada, Medicines and HealthCare Products Regulatory Authority (MHRA), Japan's Pharmaceuticals and Medical Devices Agency (PMDA), Global Health Products (MAGHP) Australia's Therapeutic Goods Administration (TGA). In addition to WLAs listed above, East African Community work sharing Initiative (EAC-MRH), Intergovernmental Authority on Development (IGAD), TMDA and Ghana FDA were also reference agencies for PPB. All three countries had a 90 days target time for the verification review.

Table 4.2: Comparison of mean approval times NASs, generics and WHO prequalified generics 2020-2023 (calend1ar days)

N/A Not Applicable

N/A1- Not Available

Country	Burundi				Kenya				Rwanda				Tanzania				Uganda				Zanzibar			
Year	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023
Full review																								
NASs	N/A	N/A	N/A	N/A					N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0	0	N/A	N/A	0	0	0	
Generics	N/A	N/A	N/A	N/A	575	739			270	270	1035	735	202	93	61	85	237	261	238	284	0	480	630	
WHO Pre-qualification	N/A	N/A	90	90	N/A	341			90	90	484	90	83	N/A	N/A	79	54	60	56	65	0	0	0	
Verification																								
NASs	N/A	N/A	N/A	N/A									N/A	N/A	N/A		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Generics	N/A	N/A	N/A	N/A									N/A	N/A	N/A		N/A1	N/A1	54	43	0	0	78	0
WHO Pre-qualification	N/A	N/A	90	90									N/A	N/A	N/A		54	60	56	65	90	90	90	
Abridged																								
NASs	N/A	N/A	N/A	N/A									N/A	N/A	N/A		N/A	N/A	N/A	N/A	0	0	0	
Generics	N/A	N/A	N/A	N/A									241	153	93						180	0	0	
WHO Pre-qualification	N/A	N/A	90	90							484	90	N/A	N/A	N/A						0	0	0	

Abridged Review (Type 2)

All six agencies conducted abridged reviews. Type 2 assessment is used by Burundi-ABREMA for selected applications such as products that have been registered by WHO, WLAs, PPB, NDA, TMDA and EAC recommended products. While Kenya, Rwanda, Tanzania and Zanzibar use abridged reviews for selected applications that were previously approved by WHO-prequalified and WLA-approved products. For Tanzania, these selected applications must be approved in at least two reference countries, and not rejected in any other reference country. Uganda utilises the abridged review pathway for Over the Counter (OTC) products. Products category reviewed by Zanzibar are NAS, major line extensions, generics and biosimilars. Kenya and Uganda had a target time of 105 calendar days, Rwanda 90 calendar days, and Tanzania 126 days (Table 4.3).

Full Review (Type 3)

All six agencies conduct type 3 assessment for all applications that do not qualify for type 1 or type 2 data assessments. Only Kenya and Tanzania conduct Type 3B (a full, independent review of pre-clinical (safety) and clinical (efficacy) is carried out) for all major applications. The other agencies conduct type 3A where data on quality, pre-clinical (safety) and clinical (efficacy) are assessed in detail but there are requirements for pre-registration elsewhere before the authorisation can be finalised (Table 4.3).

Only Burundi did not have a target time for full review of applications, but Tanzania had the lowest of 252 calendar days, followed by Uganda with 261 days, then Kenya 262 days, Rwanda 270 days, and Zanzibar with 365 days (Table 4.3). Table 4.6 further provides data for these targets with respect to major milestones.

Fast-Track/Priority Review

All six agencies conduct fast-track assessments through a priority review systems. Only Tanzania and Zanzibar indicated a target timeline of 90 and 126 calendar days respectively for review of fast-tracked applications in 2022 (Table 4.3). The agencies conduct a rapid assessment of the application to obtain pharmacological, marketing/commercialization, pharmacovigilance, and clinical trials additional information. Applicants were charged a higher fee for priority review that achieve a shorter timeline.

Table 4.3: Review models employed and target timelines (calendar days - 2022-2023)

Type of review model	Burundi	Kenya	Rwanda	Tanzania	Uganda	Zanzibar
Verifications review (type 1)	**x**	✓c	✓c	**x**	✓a	**x**
Target	N/A	90	90	N/A	90	N/A
Abridged review (type 2)	✓b	✓c	✓c	✓c	✓e	✓c
Target	N/A	105	90	126	105	126
Full review (type 3)	✓3A	✓3B	✓3A	✓3B	✓3A	✓3A
Target	N/A	262	365	180	261	365
Fast Track/Priority Review	✓	✓	✓	✓	✓	✓
Target	N/A	N/A	N/A	90	N/A	126

aFor WHO collaborative registration procedure (CRP) and EAC-recommended products.
bFor WHO CRP, WHO Listed authority (WLA)-approved and EAC-recommended products.
cFor WHO-prequalified and WLA-approved products.
dFor legacy molecules with minimal risk.
eFor OTC products

Data Requirements

The Certificate of a Pharmaceutical Product (CPP) is required with the application or before authorization is issued for all six agencies. The common technical document (CTD) format is mandatory for applications in all agencies. For all review types, all agencies required submission of full data for Modules 1-5 and Summary data for modules 2.3, 2.4 and 2.5.

The agencies then conduct a detailed assessment, and an evaluation report is prepared. Other factors considered in assessing risks and benefits were differences in medical culture/practice, ethnic factors, and national disease patterns. The agencies also endeavour to obtain internal assessment reports from other agencies such as the referenced agencies, use of public assessment reports on the internet such as the European Public Assessment Reports (EPARs) or through their participation in the WHO collaborative registration procedure where access is given for reports of prequalified products. All six agencies also have access to reports assessed through the EAC-MRH Initiative as they all participate in the EAC medicine regulatory harmonisation program. A primary scientific review is conducted by the agency staff although Tanzania include external reviewers.

Apart from Kenya and Zanzibar, the other four agencies set targets for review times spent on the scientific assessments. Only Uganda does not have a recording procedure that allows the company response time to be measured. All the agencies recognise medical urgencies and thus implement priority reviews for qualifying products. Only Tanzania conducts sequential processing of technical data. For all six agencies, physicians are less than 25% of the medical staff within the agencies' review staff. Although all the agencies have an approval times target for the overall time for the review and approval of an application (Table 4.5).

Table 4.4: Summary comparison of key features of the regulatory systems for medicines.

Marketing authorisations	Burundi	Kenya	Rwanda	Tanzania	Uganda	Zanzibar
Certificate of a Pharmaceutical Product (CPP): CPP is required with the application or before authorization is issued	✓	✓	✓	✓	✓	✓
Common technical document (CTD): CTD format is mandatory for applications	✓		✓	✓		✓
Medical staff: More than 25% within the agency review staff are physicians	x	x	x	x	x	x
Review times: The agency sets targets for the time it spends on the scientific assessment of NASs and generic applications	✓	x	✓	✓	✓	x
Approval times: The agency has a target for the overall time for the review and approval of an application	✓	✓	✓	✓	x	✓
Questions to sponsors are batched at fixed points in the review procedure	✓	✓	✓	✓	✓	✓
Company response time: Recording procedures allow the company response time to be measured and differentiated in the overall processing time	✓	✓	✓	✓	x	✓
Priority reviews: The agency recognizes medical urgency as a criterion for accelerating the review and approval process for qualifying products	✓	✓	✓	✓	✓	✓
Sequential processing: Different sections of technical data reviewed sequentially rather than in parallel	x	x	x	✓	x	x
Price negotiation: Discussion of pricing is separate from the technical review and does not delay the approval of products	x	✓	x	x	✓	✓
Sample analysis: The focus is on checking quality in the marketplace and requirements for analytical work do not delay the marketing authorization	✓	x	x	✓	✓	✓

Table 4.5: Extent of scientific assessment for full review.

	Burundi	Kenya	Rwanda	Tanzania	Uganda	Zanzibar
Chemistry, manufacturing and control (CMC) data extensive assessment				✓		✓
Non-clinical data extensive assessment	✓	✓	✓	✓	✓	✓
Clinical data extensive assessment	✓	✓	✓	✓	✓	✓
Bioequivalence data extensive assessment				✓		
Additional information obtained (where appropriate)	✓	✓	✓	✓	✓	✓
Other agencies internal review reports	✓	✓	✓	✓	✓	✓
Medical and scientific literature	✓			✓		

*A For biosimilar products not approved by a reference agency only***.**

Part III: Targets for key Milestones in the Review Process

In line with good review practices, each regulatory agency should set a target timeline for each milestone and the overall process. In the first article of this series, the review process, and key milestones for the six agencies were reported. This article reviews the target timelines for these key milestones. The standardised process map for review and approval of medical products (Figure 4.3) demonstrates key milestones that are usually recorded and monitored by mature regulatory agencies in the review of applications.

Receipt and Validation

Uganda had no target time for receipt and validation of applications. Kenya had lowest of three days, followed by Tanzania with 5 calendar days, then Rwanda with 30 days. Both Burundi and Zanzibar had 90 calendar days as their target (Table 4.6).

Queue Time

This is the time taken to start the scientific assessment after the application has been validated or accepted for review. Uganda and Kenya had the longest queue time of 365 days, followed by Burundi, Rwanda and Zanzibar with queue time ranging from 60 to 180 calendar days. Tanzania had the shortest queueing time of 35 calendar days (Table 4.6).

Table 4.6: Comparison of targets for key milestones in the full (type 3) review process - (calendar days).

Target	Burundi	Kenya	Rwanda	Tanzania	Uganda	Zanzibar
Receipt and validation (A – B)	90	3	30	5	No target time	90
Queuing (B – C)	60 -180	<365	60-150	35	365	60-180
Primary scientific Assessment (C – D)	90	No target time	No target time	100	180	180
Questions to applicant (Clock stop) (D – E)	90	180	90	60	180	180
Review by Expert Committee (G – H)	90	No target time	60	1	30	1
Approval procedure (Admin)	30-90	<30	<30	<30	30-90	<30
Overall approval time (A – I)	90	730	365	180 (exc. Applicant time	547	365

Primary Scientific Assessment

Tanzania had the shortest target for primary scientific assessment of 60 calendar days followed by Burundi with 90 days which also included peer review. Uganda and Zanzibar has 180days. Kenya and Rwanda did not have target times (Table 4.6)

Questions to Applicants

Here the clock stops as the assessment is paused and time given to the sponsor to respond to any queries. The target was 90 days for Burundi and Rwanda, and 180 days for Kenya, Tanzania, Uganda, and Zanzibar (Table 4.6).

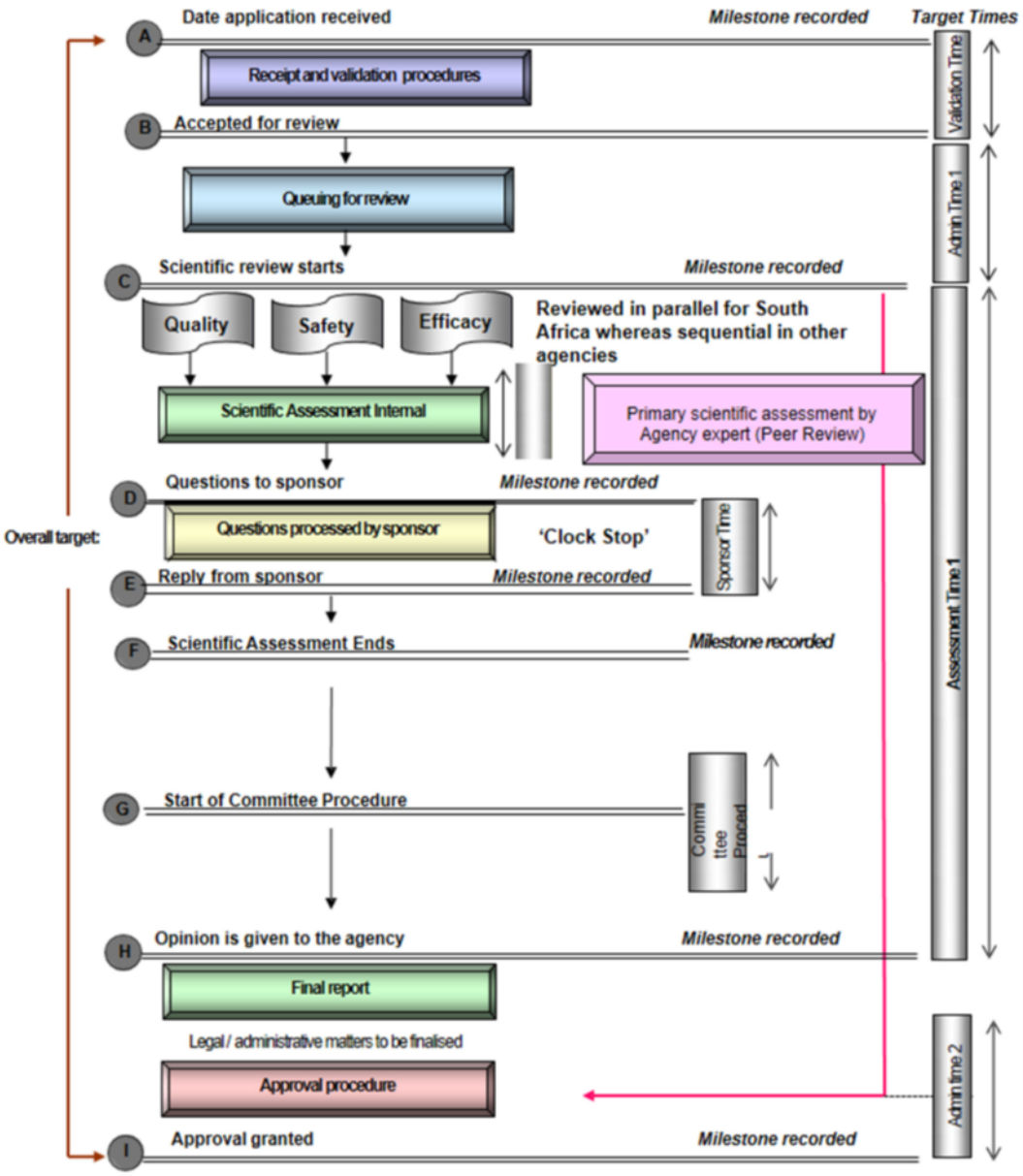
Review by Expert Committee

Four of the agencies use expert committees to make decisions on approval or refusal of marketing authorisation of medical products. Zanzibar does not use expert committees; Tanzania takes one day to make the expert committee decision while Uganda takes 30 days followed by Burundi with 90 days. Kenya and Rwanda do not have target times (Table 4.6).

Authorisation Procedure

This is the time it takes to issue the overall approval after the scientific opinion has been made. Four of the agencies (Kenya, Rwanda, Tanzania, Zanzibar) take less than 30 days. Uganda takes between 30 to 90 days, however, the sponsor is informed of a positive scientific opinion before the authorisation is issued whereas Burundi did not give a target (Table 4.6).

Figure 4.3 Standardised process map for the review and approval of medical products (adopted from Sithole et al, 2021)



DISCUSSION

The aim of this study was to compare the review models, target and review timelines as well as data requirements utilised in assessing applications for registration by countries participating in the EAC-MRH initiative to align and propose strategies for improvement. Countries with higher populations received higher numbers of applications and are also autonomous agencies. Ozawa et

al, 2019 in his studies demonstrates how improving the autonomy of health facilities improves access to essential medicines.

It is interesting to note that only one country in the region received applications for New Active substances (NAS) in 2020 and 2021. This is not surprising as several studies have highlighted a similar view that the number of NAS launched in low- and middle-income countries are very few as compared to high-income countries (Gwaza, 2016; Sithole et al, 2021). Most innovative medicines or new medicines are usually first approved by well-resourced regulatory agencies (Rago, 2008). The study by CIRS (2022) reported how six major regulatory authorities (Europe, USA, Japan, Canada, Switzerland and Australia) have used facilitated regulatory pathways and internationalisation for approvals of new medicines. It is hoped that with the operationalisation of the African Medicines Agencies (AMA), many new and complex molecules applications will be submitted through the AMA. It would be important to understand the reason for a decline in the number of applications received and approved by Burundi in 2021 as compared to 2020 and it is also important to note the decrease in mean approval times for generics in Tanzania from 202 days in 2020 to 61 days in 2022.

All the six agencies in the region are implementing reliance as the majority employ the verification and abridged review models. It is important to note that countries in this region are already relying on each other which is the major success of the EAC work sharing initiative. To enhance collaboration, it will be critical for these countries to have mutual recognition or cooperation agreements especially for Tanzania who is unable to implement the verification review due to the absence of mutual recognition agreements. It is also going to be beneficial for inter-REC reliance to be instituted for the REC-MRH Initiatives so that the different regions can also rely on the decisions of each other. This study provided a clear understanding of the review processes and regulatory requirements for registration of medical products in the agencies in East Africa. This will act as a baseline for future studies especially when there will be need to evaluate progress and identify any improvements as the African Medicines Agency (AMA) becomes operationalised. Other agencies have also been given the opportunity to better understand these review processes and can learn from each other as they share experiences.

RECOMMENDATIONS

As a result of this study, the following recommendations presented below in the order of their implementation priority should be considered by the six agencies taking part in this study.

1. **EAC-MRH as a reference agency**: All agencies participating in the EAC-MRH initiative should consider formally recognizing EAC-MRH as a reference agency for a reliance pathway.
2. **Timelines and targets:** Agencies should consider documenting all the key milestones and relevant timelines in order to monitor and measure their regulatory performance.
3. **Communication to applicants:** All agencies should communicate their regulatory requirements to applicants on their website in order to facilitate a seamless review process as well as improving timelines.
4. **Capacity building:** Agencies should consider the following:
    - Exchange of staff between agencies
    - Secondments
    - In-house education and training and continuous professional development
5. **Information system:** NRAs should develop information systems that can track registration timelines from the date the application is received to the date the registration is granted.
6. **Mutual recognition:** Develop and implement mutual recognition agreements to enhance reliance practices amongst NRAs in the region as well as inter-REC reliance.

CONCLUSIONS

This study serves as the first comparative evaluation of the review models for the national medicines' regulatory authorities of the EAC countries. It has provided a baseline for review models, target and review timelines as well as data requirements utilised in assessing applications of medical products for registration by countries participating in the EAC-MRH initiative. It is important for NRAs to have open-minded discussions, document best practices and share experiences so as to learn from each other or from reference agencies. The reliance mechanisms should be developed and implemented by the countries in the region. Implementing the recommendations from this study will enable the NRAs to align and improve their registration processes.

SUMMARY

- One of the major challenges in implementing reliance is the lack of clear registration processes in the NRAs and the delay in the approval of medical products.
- The aim of this study was therefore to compare the review models, target and review timelines as well as data requirements utilised in assessing applications for registration by countries participating in the EAC-MRH initiative so as to align and propose strategies for improvement.
- A validated questionnaire (Optimising Efficiencies in Regulatory Authorities: OpERA) which standardises and captures review processes was completed by the Head of the medicine's registration division in each of the seven EAC-MRH NRAs.
- A country report based on the completed questionnaire was developed for each NRA. These reports were then validated by the heads of the respective agencies.
- Most applications received by all countries were for generics except for Kenya which received a significant number of NAS applications
- Mean approval times for generics using full review varied with the lowest being 202 calendar days in 2020 to 61 days in 2022 in Tanzania.
- Target timelines for full review for five countries ranged between 180 calendar days to the highest 330 days.
- Only three countries (Kenya, Rwanda and Uganda) are utilising the verification review model had a target timeline of 90 days
- The targets for key Milestones in the Review Process varied for each country with a few similarities.
- All six agencies conducted abridged reviews as well as fast-track assessments through a priority review track.
- The common technical document (CTD) format was mandatory for applications in all agencies.

CHAPTER 5

REGULATORY AUTHORITY EVALUATION OF THE EFFECTIVENESS AND EFFICIENCY OF THE EAST AFRICAN COMMUNITY JOINT ASSESSMENT PROCEDURE

BACKGROUND

For almost a decade, the East African Community has implemented the Medicines Regulatory Harmonization (EAC-MRH) programme among its member states toharmonise technical requirements and standards for medical products regulation, jointly conduct scientific review of medical product dossiers to assess safety, efficacy and quality, inspect pharmaceutical manufacturing sites and streamline decision-making processes. This initiative enables the cost-effective use of limited resources and efficient and effective delivery of regulatory services to be determined, thus instilling transparency and accountability in all stakeholders, optimising the pharmaceutical market and economic development and improving access to safe, high-quality, effective medicines in the region.

The East African Community (EAC) is a regional intergovernmental organization of seven national medicines regulatory authorities (NRAs) consisting of six partner states, namely the Republic of Burundi, Republic of Kenya, Republic of Uganda, Republic of Rwanda, Republic of South Sudan and the United Republic of Tanzania. The United Republic of Tanzania is composed of the Tanzania Mainland and Tanzania Zanzibar. According to the EAC-MRH Secretariat 2021 report, all seven agencies have been benchmarked by WHO. One out of the seven NRAs is still working towards attaining Maturity Level 1, Four NRAs are at Maturity Level (ML) 1 and one NRA has attained ML3. All the seven agencies are at different levels of implementation of their Institutional Development Plans to improve their maturity levels. No NRA in the region currently has PIC/S membership, although the NDA of Uganda is preparing to apply for membership. No NRA has observer status in the ICH. Furthermore, TMDA, NDA, PPB, and Rwanda FDA have provided assessors for the WHO PQ medicines assessments (Copenhagen sessions). In addition, inspectors from NDA Uganda have worked under the WHO PQ Rotational Fellowship for Inspections.

Countries in this region have experienced the circulation of substandard and falsified medicines (Ndomondo-Sigonda et al.,2020). Currently, the prevalence of these products in Africa is estimated at 25%–30% and represents a major threat to public health, negatively impacting the growth of the African pharmaceutical sector and its overall contribution to economic development and resulting in numerous deaths (Ndomondo-Sigonda et al., 2020). According to Roth and colleagues, about 10% of medicines in low- and middle-income countries are substandard and

falsified and the lack of timely access to good quality and effective medicines has been a major challenge in Africa (Roth et al., 2018).

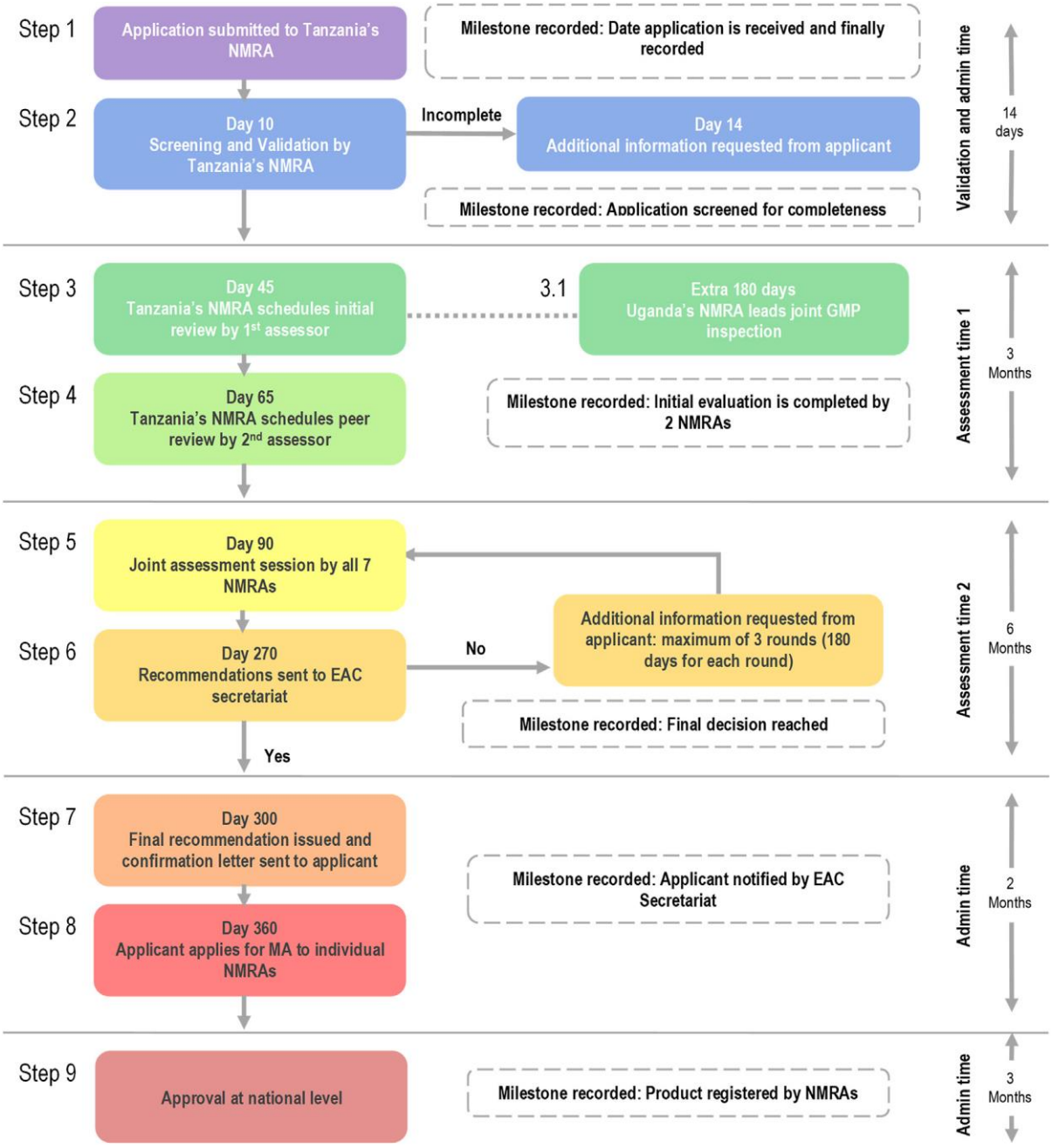
The review and registration of medical products is one of the key functions of regulatory authorities that influences access to medical products (Sithole et al., 2021a). There are several bottlenecks that impact the registration of medical products in African countries by pharmaceutical companies (Narsai et al.,2012). One of these is the lack of capacity, in which 30% of NRAs do not have the necessary expertise to conduct key regulatory functions (Keyter et al., 2020a). Hence, there is a need to strengthen medicines regulatory systems in this continent. Given the capacity differences in regulating medical products in African Member States, it is important to note that the African Union (AU)Member States and Regional Economic Communities (RECs) are making significant efforts to improve access to safe, quality, and efficacious medical products through strengthening and harmonising medicines regulatory systems. Studies show that the reluctance from companies manufacturing medical products to register their products in African markets is one of the major factors delaying access to medicines (Sillo et al., 2020). Reasons for this reluctance is due to the lengthy application process, the time, expense, and effort needed for this registration process in each NRA (Sillo et al., 2020). To improve access to safe, quality and effective medical products, the EAC joint assessment project was established in 2012, to assist in facilitating the market authorisation application process for manufacturers through a faster review of applications in the region.

A key strategy proposed by Roth and colleagues is to leverage convergence and reliance efforts (Roth et al., 2018). According to the Centre for Innovation in Regulatory Science, many NRAs are now using reliance as a mechanism to minimise duplication, maximise limited resources, build capacity and improve timely access to safe, high-quality, effective medical products (CIRS, 2021). In their study on the impact of reliance on the review process of the South African Health Products Regulatory Authority (SAHPRA), Keyter and associates showed that the introduction of reliance pathways; that is, the use of the abridged review model by the SAHPRA, led to 68% faster timelines for the approval of medicines and improved patient access to medical products (Keyter et al., 2021). Six authorities studied by Sithole and colleagues are using reliance (verification and abridged reviews) and this will hopefully improve access to medical products in these countries (Sithole et al., 2021a). Another comparative study of the registration process of the medicines control authority of Zimbabwe (MCAZ) with Australia, Canada, Singapore, and Switzerland indicated that reliance is key in agencies that rely mainly on industry fees for sustainability like MCAZ (Sithole et al., 2021b). These authorities are already demanding a high fee for applications

for products to enter the market and do not have the opportunity to increase these fees again to support resources for regulatory reviews. On the other hand, agencies with funds from government can increase resources to improve performance. Reliance is therefore a useful mechanism to assist agencies in these instances to improve regulatory performance as they will focus their limited resources on medical products that have not been reviewed elsewhere However, regulatory authorities and manufacturers might not have sufficient experience in using reliance to register new medicines as it is still a relatively new concept (CIRS, 2021).Barriers and enablers in implementing reliance models identified in a study of pharmaceutical company perceptions indicated that the main strengths were shorter approval timelines and reduced requirements. In the same study, identified weaknesses of reliance included the lack of unredacted assessment reports, long submission lag times and pathways that were not fully adopted (CIRS, 2021). In addition to these challenges for reliance, a study on reliance in South Africa, identified a lack of benefit-risk assessments; the perception that reliance would lead to loss of expertise, especially in less resourced agencies; and inadequate transparency in decision-making processes as key hurdles (Keyter et al., 2020b).

The EAC joint medicines regulatory process consists of a joint assessment of dossiers of medical products and a joint inspection of manufacturing sites. This process started in 2015 and can be described using 9 steps (Figure 5.1). Step 1 starts with the submission of the application to the lead NRA, the Tanzania Medicines and Medical Devices Authority (TMDA). In Step 2, the lead authority screens the application to check for completeness, including the good manufacturing practice (GMP) Status (Day 10). For Step 3, TMDA schedules the initial review, which also includes the GMP inspection led by the Uganda National Drug Authority (NDA; Day 45) and the GMP inspection could take another 180 days. In step 4 (day 65), an initial review is completed by two NRAs and by day 90, a joint assessment session is held (Step 5) with all representatives from the seven NRAs. At this stage a list of questions or queries are sent to the applicant when appropriate for applicant response. A maximum of three rounds is implemented, with each expected to last about 180 days. In step 6, documents are compiled and recommendations from the joint assessment are sent to the EAC Secretariat (Day 270). By day 300 (step 7), the final recommendation is issued, and a confirmation letter sent to the applicant. In step 8 (day 360), the applicant is expected to apply for marketing authorisation to individual NRAs, with approvals at national levels (step 9) and which should take place within 90 working days.

Figure 5.1 Review process map and milestones for EAC joint assessment procedure.



Unlike the approach of the European Medicines Agency (2016) where it is mandatory for countries to register medicines approved through the centralised processed, in Africa, this is not mandatory. With the launch of the EAC-MRH programme, the EAC authorities have made substantial progress in reducing timelines for registration of medical products using the joint review process. A study of the EAC-MRH pilot phase (2012–2017) by Mashingia and colleagues found that

registration timelines were reduced from 24 months to 8–12 months for products reviewed using this process (Mashingia et al., 2020). There has been a drive within regulatory authorities in recent years to re-engineer their processes for improved effectiveness and efficiency and this often begins with a baseline evaluation of the current process to identify strengths and weaknesses. Effectiveness can be defined as "doing the right thing", often measured by the value derived by customers or stakeholders of an organisation's processes or services, while efficiency can be defined as "doing the right things right", which saves an organisation time and resources. The aim of this study was to evaluate the effectiveness and efficiency of the current operating model of the EAC-MRH initiative, including the challenges it faces as well as identifying opportunities for improvement.

The aim of this study was to get the views of the individual regulatory authorities on the effectiveness and efficiency of the current operating model of the EAC-MRH initiative, including challenges faced and to identify opportunities for improvement.

STUDY OBJECTIVES

The objectives of this study were to

1) Obtain the views of the individual medicine's regulatory authorities of the EAC-MRH initiative about the performance of the joint assessment initiative to date

2) Identify the challenges experienced by individual authorities throughout the life cycle of the EAC-MRH initiative

3) Determine the strengths and weaknesses of the initiative

4) Identify the ways of improving the performance of the joint assessment initiative

5) Envisage a strategy for moving forward to improve effectiveness and efficiency

METHODS

Study Participants

The PEER questionnaire was completed by seven NRAs of the EAC joint assessment: Pharmacy and Poisons Board (PPB), Republic of Kenya; National Drug Authority Uganda (NDA), Republic of Uganda; Rwanda Food and Drugs Authority (Rwanda FDA), Republic of Rwanda; Burundi

Food and Medicines Regulatory Authority (ABREMA), Republic of Burundi; Drug and Food Control Authority (DFCA), Republic of South Sudan; Tanzania Medicines and Medical Devices Authority (TMDA) and Zanzibar Medicines and Medical Devices Authority (ZMDA) of the United Republic of Tanzania**.**

Questionnaire Development and Validation

A Process Effectiveness and Efficiency Rating (PEER) questionnaire was developed by the authors to identify the views of regulators on the benefits, challenges and opportunities for improving performance of EAC-MRH initiative and envisaging the strategy for moving forward.

Pilot Study

The PEER questionnaire (Figure 5.2) was validated by carrying out a pilot study with two authorities to establish its practicality, applicability, and content validity. Semi-structured interviews using a checklist were carried out with each authority to validate their responses to the questionnaire. The checklist had the following questions which were completed by all participants (Table 3.1).

Table 5.1: Interview Checklist - EAC PEER Questionnaire

To determine the applicability, practicality, content validity and reliability of the responses in the questionnaire, the following questions were asked during the interview.

1. Are there any questions that you did not understand?
2. Is there any information you would like to add?
3. Were the questions relevant to the objectives of the survey?
4. In your opinion, what challenges did you encounter in completing the questionnaire?
5. Are there any other benefits and challenges of the EAC-MRH initiative that you think should be included in the questionnaire?
6. What is your general observation and remarks about this study?
7. What is its impact to the EAC Joint Assessment procedure?

No changes or amendments were proposed for the questionnaire as the respondents indicated that the PEER questionnaire was adequate.

Data Collection

Using the PEER questionnaire developed by the authors, data was collected in August 2021. The main respondents were the seven assessors representing their agencies in the EAC-MRH joint assessments. The Heads of the seven agencies validated the responses by the assessors. The

interview provided flexibility and a further opportunity for the respondents, as they were able to give more open-ended answers to some questions. Some sections in the questionnaire were clarified, challenges in completing the questionnaire were discussed and the benefits of the study were acknowledged. To ensure confidentiality, the questionnaire was marked as “confidential” and participants were also informed about this during the interviews. Consent was obtained from the participants on the information that was to be shared and to minimise bias, participants reviewed the final study report. Responses and explanations were made in some sections of the questionnaire. To ensure accuracy in capturing the entire interview sessions, they were audio recorded.

Figure 5.2 EAC Joint Assessment Procedure: Process Effectiveness & Efficiency Rating (PEER) Questionnaire

Pic taken from https://www.referenceforbusiness.com/management/De-Ele/Effectiveness-and-Efficiency.html

INTRODUCTION

With the launch of the EAC-MRH programme in March 2012, Partner States have made substantial progress in reduction of timelines for registration of medical products using the joint review process. From 2012 to 2017 which has been considered as a pilot phase in a study by Mashingia et al,2020, registration timelines reduced from 24 months to 8 to 12 months for products reviewed using the new joint assessment process. Since the Boston Consulting Group (BCG) review and recommendations in 2017, there has not been a formal and structured evaluation of the regulatory performance of the EAC joint assessment procedure, although some feedback has been sought through stakeholder meetings.

In recent years, there has been a drive within regulatory agencies to re-engineer their processes for improved efficiency and effectiveness and this often begins with a baseline evaluation of the current process to identify strengths and weaknesses. *Effectiveness* can be defined as 'doing the right thing' often measured by the value derived by customers/stakeholders from an organisation's processes or services while *Efficiency* can be defined as 'doing things right' which saves the organization time and resources.

Study Participants

The PEER Questionnaire is being sent to 7National Medicines Regulatory Authorities of the EAC Partner States namely, Pharmacy and Poisons Board (PPB), Republic of Kenya, National Drug Authority Uganda (NDA), Republic of Uganda, Rwanda Food and Drugs Authority(Rwanda FDA),, Republic of Rwanda Burundi (DPML), Drug and Food Control Authority(DFCA), Republic of South Sudan ,Tanzania Medicines and Medical Devices Authority (TMDA) and Zanzibar Food and Drug Agency(ZFDA), the United Republic of Tanzania.

AIM

The aim of this study is to evaluate the effectiveness and efficiency of the current operating model of the EAC-MRH initiative including the challenges it faces as well as identifying opportunities for improvement.

STUDY OBJECTIVES

1. Obtaining the views of the individual medicines' regulatory authorities of the EAC-MRH initiative about the performance of the programme to date.

2. Identifying the challenges experienced by individual authorities throughout the life cycle of the EAC-MRH initiative.
3. Determining the strengths and weaknesses of the initiative
4. Identifying the ways of improving the performance of the work sharing programme.
5. Envisaging the strategy for moving forward

CONFIDENTIALITY

Thank you for agreeing to participate in this survey. **Your responses will be treated in strictest confidence and no identifiers of countries or respondents will be shared with any third party or made public**. External reports or presentations of the data will include only blinded results together with appropriate analytical interpretations.

The questionnaire is divided into five short sections and will take 20 minutes to complete. Thank you for taking time to complete it. We value your input!

A. DEMOGRAPHICS

1. Please state the name of your country _____

2. Please provide your responses to the following questions by writing your answer in the space provided or ticking the relevant box.

    a. Age: _____years

    b. Sex: ☐ Male ☐ Female

    c. Number of years of regulatory experience: _____years

3. What is the total number of staff in your agency? _____

4. What is the number of reviewers of marketing authorization applications? _____

5. How many reviewers participate in the EAC joint assessments? _____

6. Does your agency have a separate record of applications received for assessment under EAC-MRH? ☐ Yes ☐ No

B. VIEWS ON THE BENEFITS OF THE EAC-MRH INITIATIVE

Select your answers by ticking the relevant box(es)

1. In your view, what are 3 (or more) benefits of the EAC-MRH initiative to date?

    ☐ Leadership commitment/Governance structure
    ☐ Clear Operating Model
    ☐ Shorter timelines for approval
    ☐ Information sharing among regulators
    ☐ Building of capacity for assessments
    ☐ Sustainable resource base because of self-funding by countries
    ☐ `Harmonisation of registration requirements across the region
    ☐ Other (Please specify) _____

2. What would you say are 3 (or more) strengths of your EAC-MRH process for recommending the registration of products?

    ☐ Separate register and tracking of EAC-MRH products
    ☐ Priority review of EAC-MRH products
    ☐ Information on the submission process and timelines for EAC-MRH products are available on your country website

- ☐ Products approved under EAC-MRH are available on your country website
- ☐ Regular Committee meetings enabling timely finalisation of products after EAC-MRH recommendation
- ☐ Resource savings (time and funding)
- ☐ Pool of expert reviewers
- ☐ Other (Please specify) _____

3. How has the EAC-MRH initiative benefited member countries (regulators)?

- ☐ Training to improve the performance of the assessors
- ☐ Provides the platform for interaction and information exchange with other regulators
- ☐ Shared workload resulting in shorter timelines for approval than in individual countries
- ☐ Enables application of high standards of assessment regardless of size of country or maturity of regulatory agency
- ☐ Improved quality of dossiers submitted
- ☐ Other (Please specify) _____

4. How has the EAC-MRH initiative benefited manufacturers (applicants)?

- ☐ Reduced burden as they compile one dossier (modules 2 -5) for submission to multiple countries
- ☐ Savings on time and resources as they receive same list of questions from multiple countries enabling compilation of a single response package
- ☐ Shorter timelines for approval compared to that for the individual countries
- ☐ Access to various markets at the same time
- ☐ Other (Please specify) _____

5. How has the EAC-MRH initiative benefited patients in your country or in the EAC region?

- ☐ Quicker access to quality assured medicines
- ☐ Reduced prices of medicines
- ☐ Increased availability of medicines
- ☐ Other (Please specify) _____

C. VIEWS ON CHALLENGES OF THE EAC-MRH INITIATIVE

Select your answers by ticking the relevant box(es)

1. In your view, what are 3 (or more) challenges of the EAC-MRH initiative?

- ☐ Lack of detailed information on the process for applicants
- ☐ Low or decreasing number of applications for assessment
- ☐ Unequal workload among Partner States
- ☐ Dependence on the countries' process for communication with applicants and expert Committees
- ☐ Lack of centralised submission and tracking
- ☐ Lack of jurisdiction power
- ☐ Other (please specify) _____

2. In your view, what are 3 (or more) challenges that you face at country level in assessing/finalising EAC-MRH products?

- ☐ Inadequate human resources
- ☐ Poor record keeping and tracking of EAC-MRH products
- ☐ Lack of priority review for EAC-MRH products
- ☐ EAC-MRH work not recognized as part of agency work to be done during working hours
- ☐ Unpredictable schedule of Committee meetings

- ☐ Lack of buy-in from expert Committee(s)
- ☐ Failure by manufacturers to follow the requirement to submit the exact same dossier to all countries of interest
- ☐ Failure by manufacturers to adhere to deadlines for response to questions
- ☐ Other (Please specify) _____

3. What are the challenges faced by manufacturers submitting applications to the EAC-MRH initiative?

- ☐ Differences in time to implementation of EAC-MRH recommendations by Partner States.
- ☐ Lack of clarity about the process for submission and follow up in each Partner State
- ☐ Lack of information on country websites and the EAC-MRH website about the process, milestones, timelines, pending and approved products
- ☐ EAC-MRH process is more stringent than some country processes
- ☐ Differing labeling requirements in participating countries
- ☐ Other (Please specify) _____

D. IMPROVING THE PERFORMANCE (EFFECTIVENESS AND EFFICIENCY) OF THE WORK SHARING PROGRAMME

Select your answers by ticking the relevant box(es)

Effectiveness can be defined as 'doing the right thing' often measured by the value derived by customers/stakeholders from an organisation's processes or services while *Efficiency* can be defined as 'doing things right' which saves the organization time and resources.

1. What are 3 or more ways to improve the effectiveness of the EAC-MRH initiative in your view?

- ☐ Decision-making transparency e.g. publishing Public Assessment Reports
- ☐ Make publicly available any information that might help applicants in managing their submissions - templates of documents, lists of Q&A, timelines and milestones, disclosure of internal SOPs, etc.
- ☐ Consistency in application of guidelines and decisions
- ☐ Use of risk-based approaches e.g. reliance pathways
- ☐ Engagement and interaction with stakeholders
- ☐ Publishing of pending products
- ☐ Publishing of approved products
- ☐ Minimise the need for country specific documents
- ☐ Other (Please specify) _____

2. What are 3 or more ways to improve the efficiency of the EAC-MRH initiative in your view?

- ☐ Specific and clear requirements made easily available to applicants
- ☐ Compliance with target timelines by measuring and monitoring each milestone in the review process
- ☐ Use of robust IT systems
- ☐ Transparency on metrics and statistics e.g. % completed within timeline
- ☐ Improved central tracking of EAC-MRH products
- ☐ Improved resources e.g., number of assessors
- ☐ Centralised system for submission of applications and communication with applicants
- ☐ Other (please specify) _____

E: ENVISAGING THE STRATEGY FOR MOVING FORWARD

1. Rate the following proposals to improve the current EAC-MRH operating model from 1 – 3, number 1 representing what you think would be **most effective** in improving efficiency and number 3 the **least effective**.
Enter the appropriate number in the space provided before each proposal.

☐ To continue with the current operating model unchanged

☐ To continue with the current operating model and establish EAC integrated information management system to manage and process applications.

☐ To continue with the current operating model but provide full information on the process including timelines and milestones as well as approved products on every participating country's website and on the EAC-MRH website.

☐ The establishment of a regional administrative body to centrally receive and track EAC-MRH applications which would be responsible for allocating work, apportioning the applicable fees to countries, tracking of applications and communication with applicants.

2. In your view, would the establishment of an EAC regional medicines agency, if legally possible, be the best strategy for improved performance going forward? ☐ Yes ☐ No

   Please explain why?_____

   _____

3. In conclusion, what other strategies not previously highlighted can you think of that would strengthen the EAC-MRH initiative going forward?

Please feel free to use the comment box below to elaborate on any of your answers or to highlight questions and answers that you believe should have been included in this questionnaire.

Name of person completing the questionnaire: _____

Title (position): _____

Date: _____

Thank you for your time and help

RESULTS

For ease of understanding, the results are presented in five parts: 1) Authority resources, 2) Benefits of the EAC-MRH Initiative, 3) Challenges of the EAC-MRH Initiative, 4) Improving Performance of the work-sharing programme, and 5) Strategies for moving forward.

Part 1: Authority Resources

This part of the questionnaire provided insight into the human resources availability and size of the participating NRAs. The total number of staff for each of the seven responding agencies ranged from 33 to 338; the number of reviewers for marketing authorisation applications ranged from 4 to 50; while the number of reviewers that participate in the EAC joint assessments from these authorities ranged from 4 to 20. (Table 5.2). Only two agencies kept a separate record of applications received for assessment under EAC-MRH while five authorities did not. Reasons given for not having such a record included inadequate capacity as well as manufacturers not filing applications in all authorities for the EAC procedure. One authority reported that although they did not have a separate record, they could use their system to filter EAC applications, as segregation of applications is possible for new applications, but
the old ones must be retrieved manually as such data is not appropriately archived.

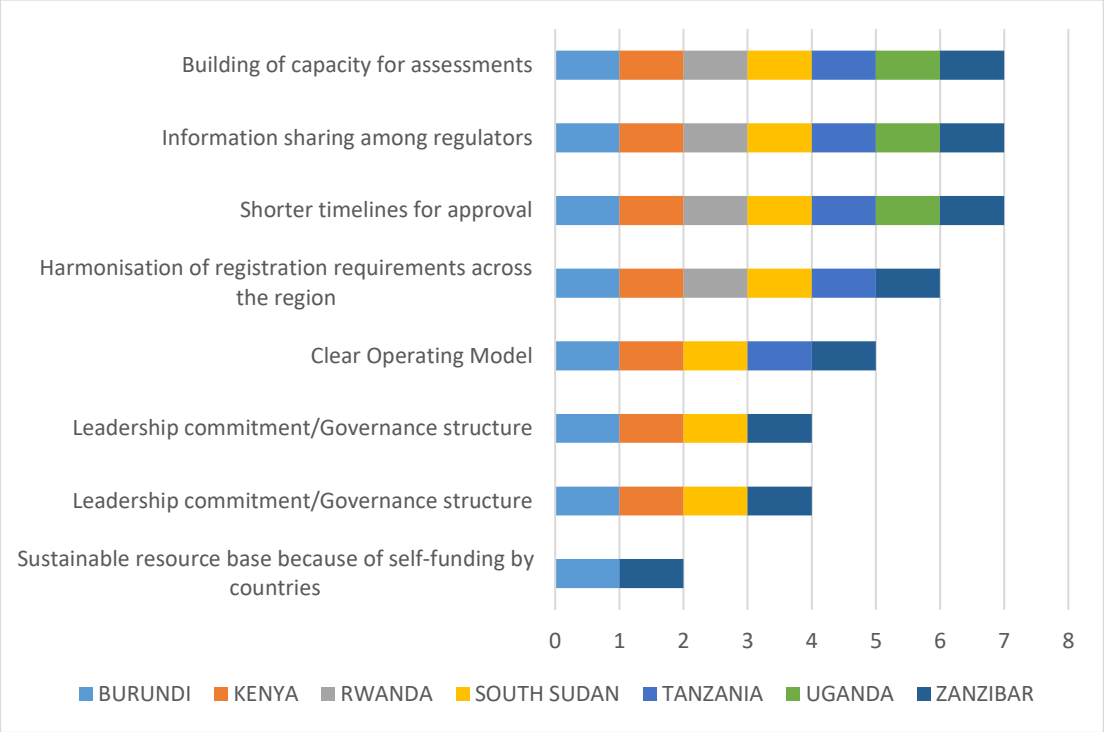
Table 5.2: National Medicines Regulatory Authority information on human resources

Measure	**ABREMA BURUNDI**	**PPB KENYA**	**Rwanda FDA RWANDA**	**DFCA SOUTH SUDAN**	**TMDA TANZANIA**	**NDA UGANDA**	**ZFDAA ZANZIBAR**
Total number of staff in your agency	33	187	196	16	338 Plus 48 temporary staff	287	150
Number of reviewers of marketing authorization applications	8	15	15	4	50	30	10
Reviewers participating in the EAC joint assessments	4	6	4	4	19	20	5

Part 2: Benefits of the EAC-MRH Initiative

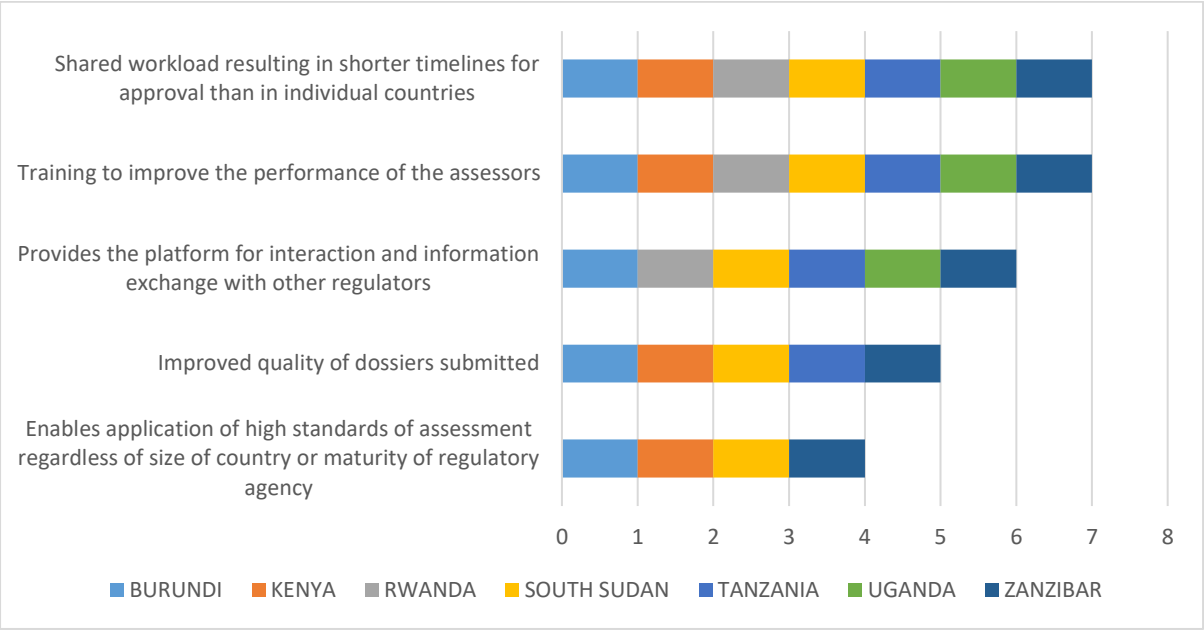
This part focused on the benefits and strengths of the joint process for recommending the registration of products to NRAs, manufacturers, and patients.

Figure 5.3 Benefits of the EAC Initiative



Shorter timelines for approval, information sharing among regulators, and building capacity for assessments were highlighted by all seven authorities as the main benefits of the EAC initiative (Figure 5.3). Building capacity for assessments was indicated by all as a considerable benefit, which was especially apparent in less-resourced agencies. Some agencies alluded to the fact that they never had assessors before the EAC-MRH but now have been able to rectify their situation because of the EAC joint assessment process. Harmonisation of registration requirements across the region was another benefit selected by six NRAs. Leadership commitment had improved significantly because of the collaboration with EAC, World Health Organization (WHO) and NRAs. All NRAs indicated that they have a pool of expert reviewers and this and the priority review of EAC products were the strengths of the EAC process at a country level. Regular committee meetings enabling the timely registration of products after EAC recommendation was another strength (5/7) while four NRAs indicated resource savings were a benefit.

Figure 5.4 Benefits of the EAC initiative to countries (regulators)



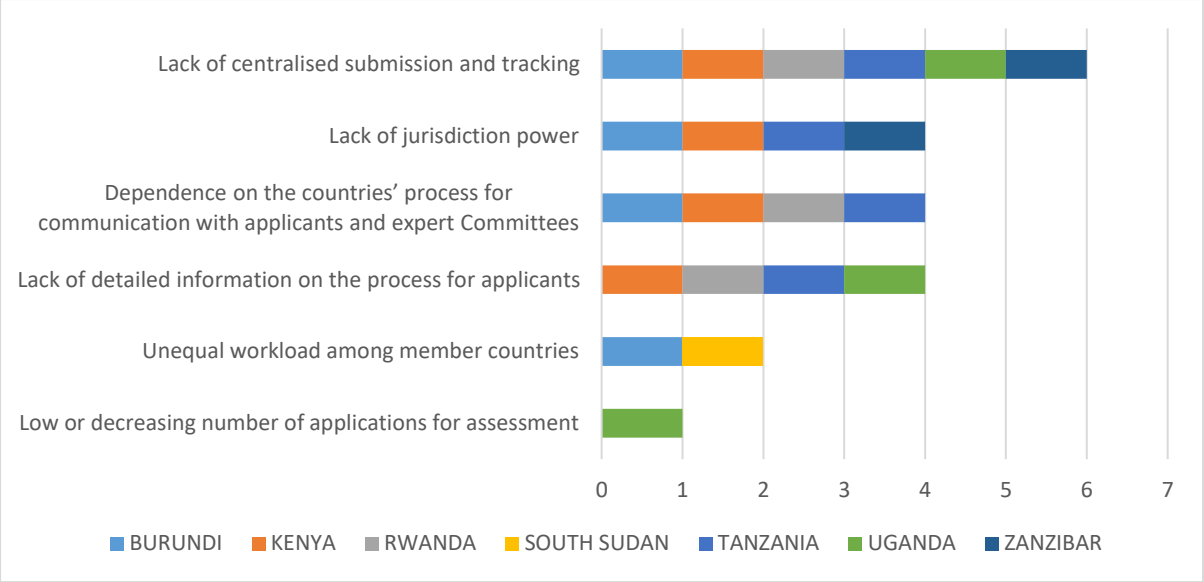
This initiative has benefitted regulators in training, improved the performance of assessors and facilitated shared workloads, resulting in shorter timelines for approval than in individual countries. It has also provided a platform for interaction and information exchange with other regulators. However, this interaction occurs only during assessment sessions and there is no post-assessment exchange (Figure 5.4).

There is a reduced burden for applicants, who compile only one dossier (modules 2–5) for submission to multiple countries and receive the same list of questions from multiple NRAs, enabling the compilation of a single response package, leading to savings in time and resources. Shorter timelines for approval compared with that of individual countries has enabled access to various markets at the same time. The EAC-MRH procedure has allowed quicker access to quality-assured medicines and increased the availability of medicines for patients in the region. However, this initiative has not reduced the prices of medicines, as some generic products still maintain high prices. Furthermore, because applicants do not always apply to all agencies participating in the EAC-MRH joint assessment, the benefits of the EAC initiative for patients will only apply to some NRAs in the region.

Part 3: Challenges of the EAC-MRH Initiative

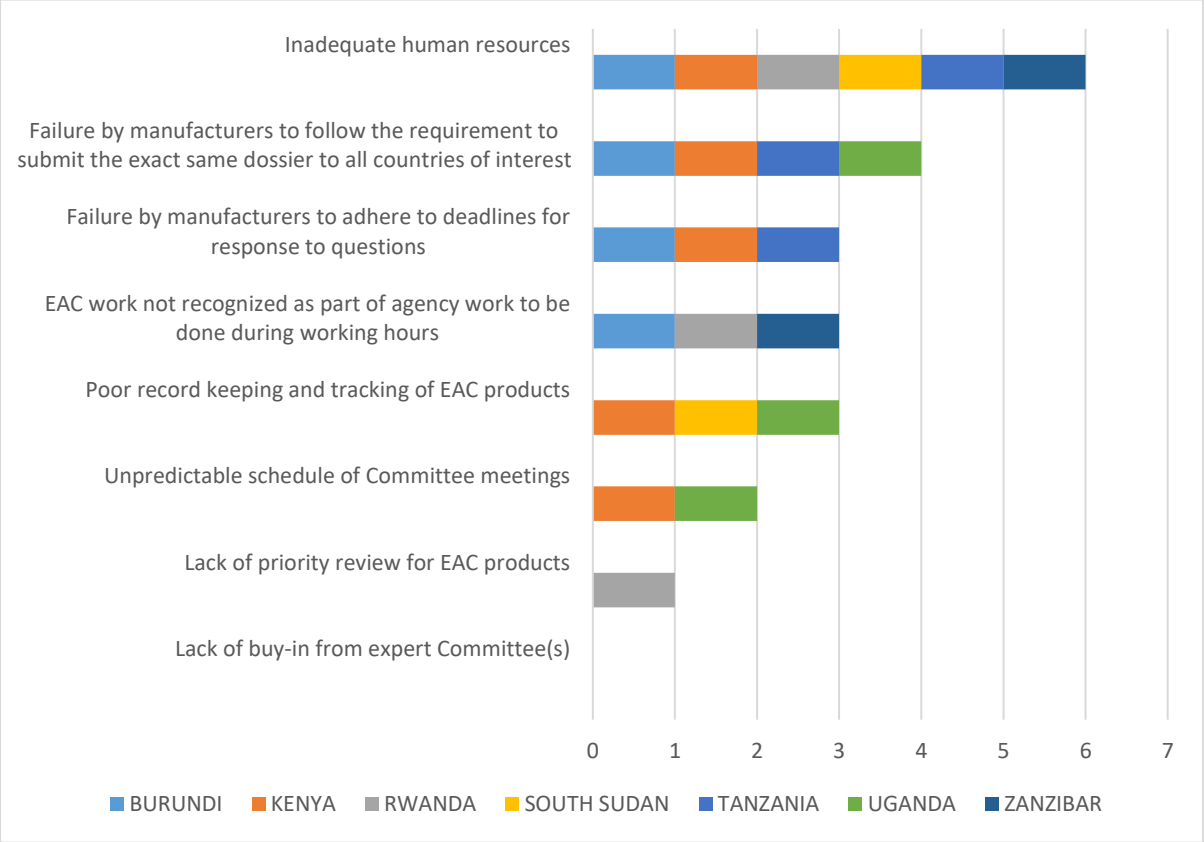
The major challenge to the initiative identified by the authorities is the lack of a centralised submission, jurisdiction power and tracking system. Also, as mentioned, manufacturers may only apply to NRAs in their countries of interest. The initiative depending on the countries' processes for communication with applicants and expert committees was another challenge.

Figure 5.5 Challenges of the EAC-MRH Initiative



The lack of detailed information on the process for applicants was expressed by four respondents, with the concern that applicants sometimes apply to both the EAC and to the NRA. One NRA respondent indicated unequal workloads among the NRAs as a challenge, as dossiers are allocated to the well-resourced NRAs while less-resourced NRAs are given query responses from applicants to process. These assignments are necessary because new applications and complex dossiers cannot be assessed by the less resourced NRAs, but they result in an increased workload for authorities with greater resources compared with those that are less resourced. Lack of sharing of consolidated (aggregated) information by the lead country, particularly for consolidated assessment reports was also cited as a major challenge. Assessors often struggle to get reports after the assessment sessions are completed, because, although there is an assumption that countries safely retain reports after assessment, this is not the case (Figure 5.5).

Figure 5.6 Challenges assessing EAC-MRH products at country level.



Following an interview, one of the respondents stated that: "Only the list of products approved are shared without the report. This delays the process of registration in order to get the report as it is needed for national registration". Most NRAs mentioned inadequate human resources as the key challenge at a country level and even one of the well-resourced NRAs expressed the need for more assessors to adequately handle the number of applications received for assessment.

Failure by manufacturers to follow the requirement to submit the exact same dossier to all countries of interest is also a major challenge for authorities. Poor record keeping and tracking of EAC-MRH products at a national level is another hurdle for some agencies, as they do not maintain a separate record of applications received for assessment under EAC-MRH programme, and applicants sometimes submit applications for joint review to the EAC and then submit the same application at a national level. This creates duplicative communication, with parallel assessments conducted at both country and regional levels.

The unpredictability of applications causes scheduling inefficiencies, sometimes warranting the convention of unscheduled meetings to cover unanticipated applications or the postponement of scheduled meetings if enough have not been received.

Although the EAC-MRH work can provide learning experience to assessors, it is not recognised as part of regulatory authority work to be carried out during working hours, which was seen by

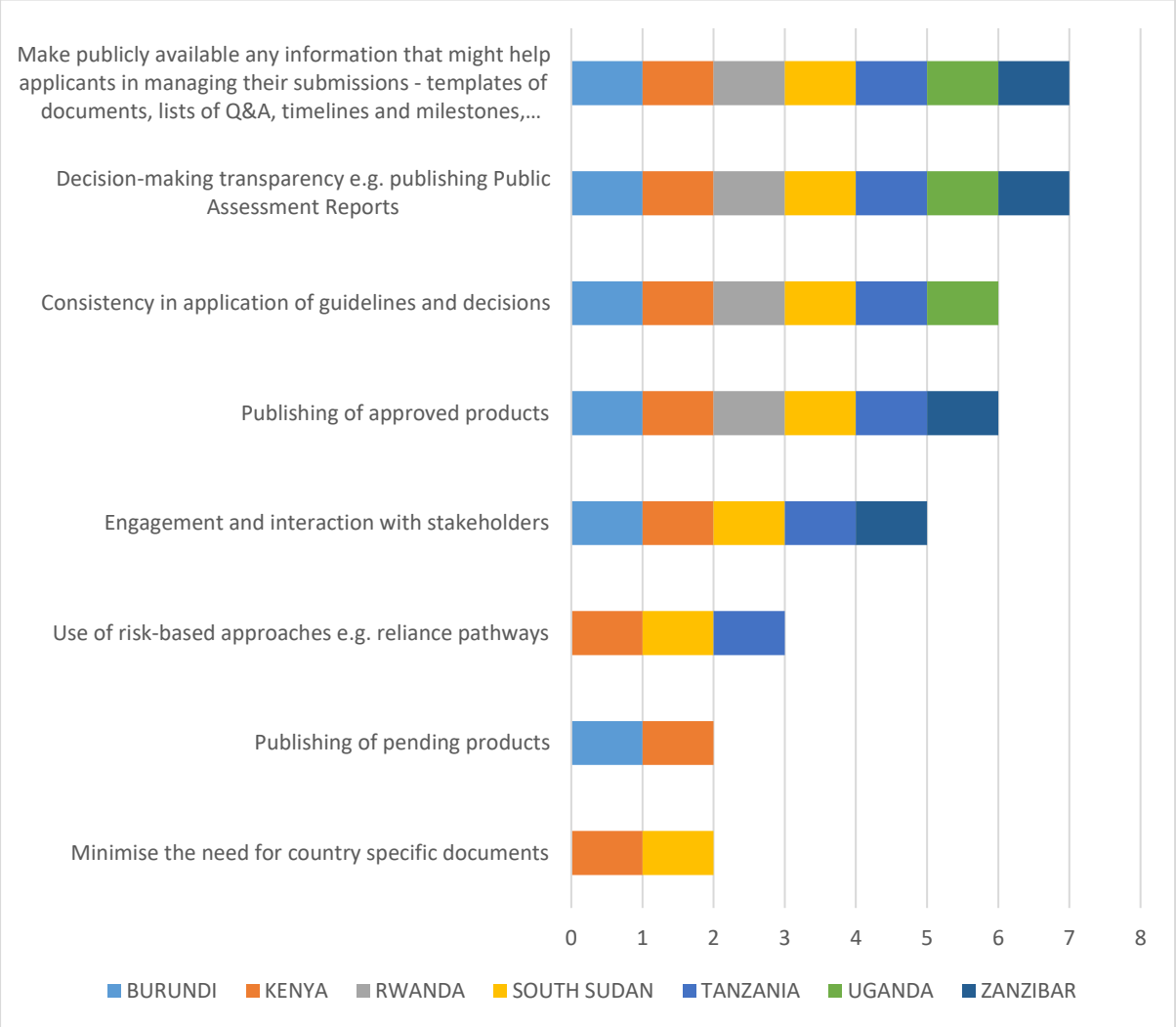
authorities as an issue. Failure by manufacturers to adhere to deadlines in response to questions is a challenge and due to this delay, some NRAs may provide marketing authorisation without the nomination of the local technical representative by the manufacturer as required (Figure 5.6). Because the EAC conducts a stringent assessment, applicants may apply to less stringent countries (NRAs) to get their products registered. However, applicants do not have full information on the application process, as there is no guidance on how to submit applications on the EAC website and there is lack of clarity about the process for submission and follow up in each NRA. Applications should go to the lead NRA for EAC assessments, but some applicants still send applications to other NRAs. There are significant differences in time to the implementation of EAC-MRH recommendations by the NRA which could be caused by the lack of a centralised system for payment of the application fees to all EAC NRAs. Finally, differing labelling requirements in participating countries was also highlighted as one of the challenges faced by applicants.

Part 4: Improving the Performance (Effectiveness and Efficiency) of the Work-Sharing Programme

Determining the views of the regulators in improving effectiveness and efficiency of the EAC-MRH initiative was an important part of this study. The top three ways to improve effectiveness identified by respondents were 1) decision-making transparency; for example, publishing public assessment reports or making any information publicly available that might help applicants in managing their submissions such as templates, lists of questions and answers, timelines and milestones; 2) disclosure of internal SOPs; and 3) consistency in application of guidelines and decisions (Figure 5.7).

Other suggestions for improvement included ensuring good record keeping for application and report traceability and sharing access to the consolidated assessment reports and query responses with NRAs by the host country NRA. The host country for GMP should also share inspection reports with the EAC secretariat, sharing product approval letters with the focal persons. This information should be uploaded to the portals in order to facilitate compliance with NRA requirement for proof of how products are approved through the EAC procedure. This information is typically provided to the applicants, but a copy should also be requested to be sent to the NRA to assist scheduling of the final committee meetings at the national level.

Figure 5.7 Ways to improve effectiveness of the EAC-MRH initiative.



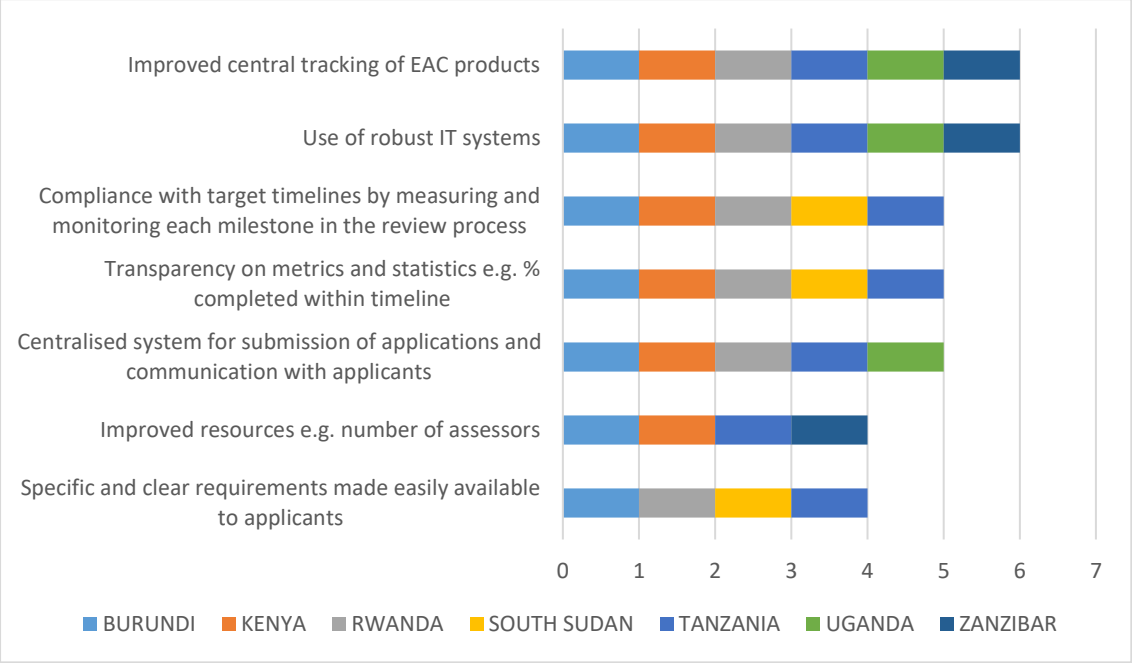
The top five ways identified to improve the efficiency of the EAC initiative were (Figure 5.8) 1) improved central tracking of EAC products; 2) the use of robust IT systems; 3) compliance with target timelines by measuring and monitoring each milestone in the review process; 4) transparency on metrics and statistics and 5) a centralised system for submission of applications and communication with applicants.

Part 5: Strategies for Moving Forward

The following proposals were suggested to improve the EAC operating model. First, continue with the current operating model and establish an EAC integrated information management system to manage and process applications; second, continue with the current operating model but provide full information on the process, including timelines and milestones as well as approved products on every participating country's website and on the EAC website. The third option, to continue

with the current operating model unchanged was not considered appropriate. Other strategies were proposed that would strengthen the initiative going forward.

Figure 5.8 Ways to improve efficiency of the EAC-MRH initiative.



Capacity building

The EAC should support and work closely with less-resourced regulatory authorities to build their capacity to the level of better resourced NRAs in the region. Following an interview, one of the respondents stated that: "A major request here is for the EAC to facilitate the process of weak NRAs in order to improve from the basic to the intermediate level and so they eventually become experts". The NRAs should be supervised after the joint review processes to make sure they are doing the right thing. Although the expectation is that the EAC experts are well versed with regulatory subject matters after training, this is not always the case, and supervision may still be needed. In addition, training is currently needed for new assessors as many trained experts have left their agencies. Finally, the EAC joint assessment should be included among the workload of the authority to avoid delays in the assessment process.

Improving work and information sharing

Improved communication within the EAC NRA is critical and this can be achieved by sharing the final assessment reports of the approved products with all NRAs. Because authorities must access the reports for the national registration process, sharing only the list of approved products without the reports results in unnecessary delays. The development of a robust IT system for the EAC-

MRH that can be used for tracking and uploading dossier as well as a repository for reports is required. Apart from Tanzania NRA, the agencies in the region do not have an appropriate IT infrastructure, although Kenya is in the process of developing such a system. The availability of financial or technical support will assist the development of an efficient information management system.

EAC–MRH coordinating mechanism

The authorities agreed that the EAC-MRH coordinating mechanism at the secretariat level should be strengthened. Legal procedures should be developed to enable the EAC secretariat to perform some functions such as the collection of fees and charges for joint activities that are not currently performed by NRAs such as active pharmaceutical ingredient master file certification procedures and inspection of clinical research organisations. Regularly sharing research findings, providing regulatory training, and the exchange of experts for mentorship, coaching and capacity building of EAC NRAs would be helpful. The need for all seven NRAs in the region to be operating with similar standards is an important objective for developing competency. Experience has shown that manufacturers take applications to agencies with lower standards, as they will request fewer requirements and make the process easier than the EAC process. Therefore, it is important that NRAs in the region have the same standard as the EAC-MRH process. All NRAs in the region should encourage more companies to embrace the EAC-MRH initiative.

Establishing a regional authority

Establishing a regional authority was reported to be the best strategy for improved performance, as it would promote innovation and access to new technologies; ensure all EAC NRAs have access to high quality, safe and effective medicines; improve the quality of medicines and reduce sub-standard and falsified products in the region as well as improve regulatory expertise across the EAC; provide a global overview of the different regulatory developments at national and international levels as well as facilitating information sharing and best practices among regulatory experts. The reasons for not establishing a regional authority cited by some respondents included a need to strengthen the regulatory systems for all the EAC NRAs. As many of the authorities depend on the fees collected from the applicants to fund their operations, distributing the fees among the members states if the regional authority was established would present a challenge. It was further suggested that the region is not sufficiently mature yet for a regional agency; however, by establishing the EAC regional medicines authority, capacity building and existing collaboration among countries might be maximised. It was also stated that the establishment of EAC regional

medicines authority is not necessary as the African Medicine Agency (AMA) will soon be coming into force; however, the mandate for the AMA depends on the support of the regional agencies. It is understood that the AMA will be regulating only complex molecules while NRAs and Regional Agencies will continue with evaluation of other essential medical products. Therefore, the AMA is not replacing the NRAs, but will complement and support their work.

DISCUSSIONS

The aim of this study was to evaluate the effectiveness and efficiency of the current operating model of the East African Community Medicines Regulatory Harmonisation initiative including the challenges it faces as well as identifying opportunities for improvement. The NRA acknowledged that the initiative has been of considerable benefit as it has moved toward achieving its main objectives, which are shorter timelines for approval of medicines, the existence of information sharing among regulators and building capacity for the agencies. The timely registration of products after an EAC recommendation has been enabled by regular EAC committee meetings, shared workloads and the creation of a pool of expert reviewers, which has led to resource savings. Also, allowing applicants to compile one dossier for submission to multiple countries has enabled the industry to have simultaneous access to several markets. The strengths of this initiative have resulted in quicker access and increased availability of quality-assured medicines for patients in the region. The median time for joint assessment in 2019 was reported to have decreased to 240 working days, demonstrating that the EAC joint assessment process was becoming more efficient (Mashingia et al., 2020). In the same study, registration timelines at the national level were reduced from 24 months to 8–14 months during the 2012–2017 time period (Mashingia et al., 2020). Giaquinto and colleagues also confirmed that one of the strengths of this initiative was the implementation of the joint assessment and work-sharing procedure with the introduction of the submission of one dossier by applicants to all EAC authorities (Giaquinto et al., 2020). The twinning programme was also identified as one of the key strengths of this initiative (Giaquinto et al., 2020).

However, several key challenges were identified that have affected the full realisation of the benefits of this initiative. They include the lack of a centralised submission and tracking system, with most agencies not having separate records of applications received for assessment under EAC-MRH, inadequate human resources, failure by manufacturers to follow the requirement to submit the exact same dossier to all countries of interest, lack of information on country or EAC

websites, poor record keeping and tracking of EAC products, assessors not having access to reports after the joint assessment sessions, and the EAC-MRH work not recognised as part of the respective national authority workload.

The outcome of this study also has confirmed the findings from other authors. In a pilot study of the EAC-MRH, Mashingia and associates identified numerous challenges faced by the EAC harmonisation initiative. These included the difficulty for applicants tracking the progress of their applications as the system is not transparent in terms of timelines; inadequate follow-up to questions by both applicant and NRAs; delays in some products being granted marketing authorisation at the national level after the regional approval has been made; financial sustainability as well as submission of applications and fees by manufacturers to all EAC NRAs after the joint review process (Mashingia et al., 2020). Different capacities of NRAs affects trust, as sometimes authorities tend not to rely on the decisions of the new authorities in the region. Whilst harmonisation has had some benefits, it has impacted the less mature agencies who have not specialised, as they tend to rely on the mature agencies instead of building their own expertise. Other barriers highlighted in the study were lack of a legally binding framework amongst the NRA in the EAC; understaffing and staff turnover and less involvement by the heads of agencies in shaping the agenda of the harmonisation programme (Mashingia et al., 2020).

To address some of the weaknesses and improve effectiveness and efficiency, it is suggested that the use of a robust IT system to improve the central tracking of EAC products is essential. Ensuring the availability of information on decision-making transparency on the websites (national and regional) and establishing one central point for payment would also make the process faster. The lesson to be learned from the European Medicines Agency is that registration of medicines approved through the central process should be mandatory. With only one NRA in the region that operates at maturity level 3, improving the capacity of assessors as well as work and information sharing and the coordination mechanism for the regional joint assessment programme with the eventual establishment of the regional medicine's authority would be key strategies for moving forward. The African Medicines Agency treaty came into force on 5th November 2021 after the 15th ratification instrument was deposited at the African Union Commission. Two EAC member states have ratified the AMA treaty. One of the mechanisms being put in place to operationalise AMA is the building of regulatory work force. The African Medicines Regulatory Harmonisation Initiative has been leading the work force development through the establishment of Regional Centres of Regulatory Excellence (RCOREs) and the medicines regulatory harmonisation

programmes (Ncube et al., 2021). Giaquinto and colleagues are also of the view that transparency, responding to feedback from industry, meeting registration timelines, reliance and utilising metrics would further improve access to essential medical products in the region (Giaquinto et al., 2020).

Charging its own fees as the initiative increases its scope and making joint regulatory decisions mandatory would assist in sustaining the initiative (Giaquinto et al., 2020). In their study on the evaluation of the review models and approval timelines of countries participating in the Southern African Development Community Medicines Regulatory Harmonization (SADC-MRH) project, Sithole and associates recommended that national regulatory systems be strengthened to equip them to fully participate in reliance initiatives such as Zazibona (Sithole et al., 2021a). This recommendation would also apply to the EAC-MRH joint assessment procedure, as countries in this region work towards relying on the reviews and decisions made by other agencies to fast-track access to safe, high-quality and effective medicines by patients. The opportunity to implement a reliance strategy by regulatory authorities would improve transparency and accountability and take advantage of regulatory decisions through the utilisation of assessment reports. According to Keyter and colleagues, published assessment reports should include information on how the regulatory authority has analysed the benefits and risks of the medical product and made their final decision. The study recommends the use of a standardised approach to public assessment reports to improve communication on benefit risk assessment, which in turn would support any reliance initiatives (Keyter et al., 2020a).

Arik and colleagues also proposed several approaches in the EAC Road Map 2020–2022 to address the challenges encountered in implementing the EAC-MRH project. These included having Regional Technical Officers, who are fully dedicated to regional activities, unlike the usual practice, in which NRA staff have had to take part on an ad hoc basis, with insufficient time allocated for regional activities, the establishment of a cooperation agreement, the introduction of a coordination fee to support regional assessments and inspections, as well as the expansion into new product areas (biologics, biosimilars) should be considered. A major proposal in the road map was the establishment of single autonomous authority for the region (Arik et al., 2020).

RECOMMENDATIONS

The key recommendations in this study to improve effectiveness and efficiency of the EAC-MRH joint assessment are presented below in the order of their implementation priority:

1) Measuring and monitoring timelines—The development of an integrated system for tracking applications for the regional initiative to monitor registration timelines of the products. NRAs should take full responsibility for tracking applications and recommended products for the EAC joint procedure. Also, an internal portal for information sharing by the assessors should also be made available to enhance post assessment session interactions by regulators. This portal should also be used as a repository for reports. In addition, target timelines should be established for all the milestones including review time and applicant response time.

2) Availability of submission guidelines—The existing EAC-MRH programme and NRA websites should be enhanced with clear guidelines on the process of submission for the EAC procedure and follow up by each authority to improve the application
process, transparency, accountability, and communication.

3) Training and capacity building–Continuous training of assessors should be conducted, as it would lead to staff retention and improvement in motivation, especially as there is high staff turnover within the authorities. The twinning programme should be reinstated, as it was of great benefit to the less resourced agencies.

4) The EAC-MRH coordination process–This should be strengthened to improve programme implementation and achieve the expected results. Sensitisation and awareness campaigns should be conducted to encourage manufacturers to utilise the EAC-MRH procedure. Process of payment of fees by applicants should be addressed with the establishment of one central point for payment and decision making, which would make the process faster. Dedicated full-time staff should be appointed for the assessment of regional dossiers and the sustainability of the initiative will be enhanced if more technical officers are appointed.

5) Initiation of a longitudinal study–this would enable collection of efficiency and effectiveness data in order to demonstrate change (i.e., improvement) over time.

6) Regional Medicine Authority—The EAC Secretariat should reconsider the decision to establish a Regional Medicines Agency.

CONCLUSIONS

All agencies expressed the importance of the EAC-MRH work sharing initiative, especially with the current limited resources. The relevance of this initiative in the region cannot be

overemphasised, as it has enabled the regulatory institutions in the region with limited resources to continue to fight both substandard and falsified medical products and technologies. With the establishment of the African Medicines Agency, there is great hope that this continental authority will help shape the regional agencies. The EAC NRAs, African Union institutions, development partners and all stakeholders should be called on to mobilise resources that can improve the effectiveness and efficiency of the EAC joint assessment procedure. According to Ndomondo-Sigonda and colleagues, the problem of substandard and falsified medical products in Sub-Saharan Africa can only be addressed if the National Medicines Regulatory Authorities have the necessary support from their national governments and the public as well as a legal mandate to manage the regulation of medical products with the necessary human and financial resources (Ndomondo-Sigonda et al., 2020). To continuously improve this work-sharing and reliance initiative, the above key recommendations would need to be implemented at both national and regional levels.

SUMMARY

- The aim of this study was to obtain the views of the individual regulatory authorities on the effectiveness and efficiency of the current operating model of the EAC-MRH initiative, including the challenges faced and to identify opportunities for improvement.

- The East African Community has implemented the Medicines Regulatory Harmonization (EAC-MRH) programme among its seven member states for over ten years.

- Using the Process Effectiveness and Efficiency Rating (PEER) questionnaire developed specifically for this study, data was collected from the seven countries (Kenya; Uganda; Rwanda; Burundi South Sudan; Tanzania and Zanzibar)

- The key benefits of the EAC initiative as indicated by the seven agencies resulted in a shared work load, shorter timelines for approval, a platform for interaction and information sharing among regulators, building capacity for assessments, harmonisation of registration requirements across the region, and a reduced burden for applicants.

- Major challenges to the initiative identified by the authorities is the lack of a centralised submission, jurisdiction power and tracking system, a lack of detailed information as well as inadequate human resources and failure by manufacturers to follow the requirements to submit the exact same dossier to all countries of interest.

- The authorities agreed that the EAC-MRH coordinating mechanism at the secretariat level should be strengthened as well as establishing a regional autonomous agency was reported to be the best strategy for improved effectiveness and efficiency.

CHAPTER 6

PHARMACEUTICAL INDUSTRY EVALUATION OF THE EFFECTIVENESS AND EFFICIENCY OF THE EAC-MRH INITIATIVE

BACKGROUND

Countries need fully functional regulatory systems in order to respond to public health needs as well as to enhance access to safe and effective medicines (Kusinitz Met al., 2017). One of the determinants of access to essential medicines is regulatory filing and registration (Sillo et al., 2020). In Africa, regulatory authorities face several challenges in regulating medicines, as most national medicines regulatory authorities (NMRAs) are not adequately resourced when compared with established regulatory authorities. As of 2022, only five NMRAs in Africa, Ghana, Tanzania, South Africa, Egypt and Nigeria have attained the World Health Organization (WHO) maturity level 3 status; that is, a stable, well-functioning regulatory authority (Broojerdi, 2020). Since 2009, the African Union Development Agency (AUDA-NEPAD) has been spearheading the African Medicines Regulatory Harmonisation (AMRH) initiative as a means of improving access to safe, high-quality and effective medicines in Africa through the harmonisation of regulatory requirements (Dansie et al., 2019). Including the East African Community Medicines Regulatory Harmonisation (EAC-MRH) programme, five regional harmonisation initiatives have been established in Africa to increase the number of quality-assured products available to patients, by simplifying the registration processes for manufacturers and improving capacity (Sillo et al., 2020; Ndomondo-Sigonda et al., 2021).

The EAC-MRH Initiative

The EAC-MRH initiative is a joint assessment procedure composed of seven NMRAs in the EAC region. These NMRAs include Burundi Food and Medicines Regulatory Authority (ABREMA), Bujumbura, Burundi; Kenya Pharmacy and Poisons Board (KPPB), Nairobi, Kenya; National Drug Authority (NDA), Kampala, Uganda; Zanzibar Medicines and Medical Devices Agency (ZMDA), Zanzibar, Tanzania; Drug and Food Control Authority (DFCA), Juba, South Sudan; Rwanda Food and Drugs Authority (RFDA), Kigali, Rwanda; and Tanzania Medicines and Medical Devices Authority (TMDA), Dar Es Salaam, Tanzania. To provide guidance to the NMRAs in managing applications for registration of human medicinal products in the EAC, a compendium was developed in 2014 by the Technical Working Group (TWG) on Medicines Evaluation and Registration (MER) of the EAC-MRH Project. The compendium has five modules and sets out procedures and requirements for the implementation of Pharmaceutical Products Registration through established Common Technical Documents (CTD) within EAC NMRAs. These documents are based on the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical Products for Human use (ICH) guidelines. The

aim of the CTD guidelines is “to provide harmonised medicines registration procedures using the CTD in order to improve access to essential medicines for prevention and treatment of priority disease conditions in the East African region” (EAC Secretariat, 2014). According to Sithole et al. (2022), the CTD format has helped to improve work sharing and the harmonisation of registration requirements and joint reviews in Africa.

With the launch of the EAC-MRH programme in March 2012, member countries have made substantial progress in the reduction of timelines for registration of new medicines using the joint review process. The aim of the regional harmonisation project is to minimise barriers to medicine registration and eventually increase the number of products registered within a shorter timeline. Mashingia and others (2020) reported that from 2012 to 2017 registration timelines were reduced from 24 months to 8–12 months for products reviewed using the new joint assessment process. Started in 2015, the EAC initiative has a decentralised structure, with focus on work sharing and reliance. It is composed of a joint assessment of dossiers for medical products submitted by applicants for review and a joint inspection of manufacturing sites by the assessors (Sillo et al., 2020). As outlined by Ngum and associates (2022), this process has nine steps, starting with the submission of an application and ending with approval at a national level, which is expected to occur within 90 days after a positive recommendation is made. As of December 2021, a total of 159 applications have been received, 144 assessed and 79 products recommended for registration through the EAC-MRH joint procedure, with a median time for recommendation to market authorisation between 30 and 90 days (AUDA-NEPAD, 2021).

A study was conducted in 2021 to determine the views of regulators from the seven NMRAs of the EAC-MRH initiative on the effectiveness and efficiency of the work-sharing initiative. One of the recommendations from this study was to conduct a similar study with the applicants, so that there could be a comparison of the benefits and challenges from the point of view of both key stakeholders (Ngum et al., 2022). The aim of this study was, therefore, to evaluate the effectiveness and efficiency of the current operating model of the EAC-MRH initiative from the applicants’ perspective, including the challenges it faces as well as to identify opportunities for improvement.

STUDY OBJECTIVES

The study objectives were to:

1. Obtain the views of the applicants of the EAC-MRH initiative about the performance of the programme to date
2. Identify the challenges experienced by applicants throughout the life cycle of the EAC-MRH initiative
3. Determine the strengths and weaknesses of the initiative
4. Identify the ways of improving the performance of the work-sharing programme
5. Envisage the strategy for moving forward.

METHODS

Study Participants

From the 34 applicants identified as using the EAC-MRH initiative to submit applications for registration and marketing authorisation, 25 were determined to be eligible for the study; among this group there were 11 non-responses, leading to a 56% response rate. Study participants were distributed into three categories; Generics (foreign); that is, applicants who manufacture generic medicines outside of the EAC region, Generics (local); that is, applicants who manufacture generic medicines within the EAC region, and Innovators; that is, applicants who submitted applications for registration of innovator medicines. During the period of study (2015–2021), there were no local innovators that submitted applications for innovator medicines for registration.

Development of the PEER-IND Questionnaire

The authors developed a Process Effectiveness and Efficiency Rating for Industry (PEER-IND) questionnaire to identify the views of applicants on the benefits, challenges and suggestions for improving the performance of the EAC-MRH work-sharing initiative. PEER-IND comprised five parts; Demographics; Benefits of the EAC-MRH initiative; Challenges of the EAC-MRH initiative; Improving the performance (effectiveness and efficiency) of the work-sharing programme and envisaging the strategy for moving forward.

Pilot Study

The PEER-IND questionnaire (Figure 6.1) was validated by carrying out a pilot study with two applicants to establish its practicality, applicability, and content validity. Semi-structured interviews using a checklist (Supplementary Material S2) were carried out with each authority to

validate their responses to the questionnaire. The checklist had the following questions which were completed by all participants (Table 6.1).

Table 6.1: Interview Checklist - EAC PEER Questionnaire

To determine the applicability, practicality, content validity and reliability of the responses in the questionnaire, the following questions were asked during the interview.

1. Are there any questions that you did not understand?
2. Is there any information you would like to add?
3. Were the questions relevant to the objectives of the survey?
4. In your opinion, what challenges did you encounter in completing the questionnaire?
5. Are there any other benefits and challenges of the EAC-MRH initiative that you think should be included in the questionnaire?
6. What is your general observation and remarks about this study?
7. What is its impact to the EAC Joint Assessment procedure?

No changes or amendments were proposed for the questionnaire as the respondents indicated that the PEER questionnaire was adequate.

Figure 6.1 EAC Joint Assessment Procedure: Process Effectiveness & Efficiency Rating (PEER-IND) Questionnaire

EAC JOINT ASSESSMENT PROCEDURE

PROCESS EFFECTIVENESS & EFFICIENCY RATING (PEER-IND

Pic taken from https://www.referenceforbusiness.com/management/De-Ele/Effectiveness-and-Efficiency.html

PEER-IND QUESTIONNAIRE

INTRODUCTION

With the launch of the EAC-MRH programme in March 2012, Partner States have made substantial progress in reduction of timelines for registration of medical products using the joint review process. From 2012 to 2017 which has been considered as a pilot phase in a study by Mashingia et al,2020, registration timelines reduced from 24 months to 8 to 12 months for products reviewed using the new joint assessment process. Since the Boston Consulting Group (BCG) review and recommendations in 2017, there has not been a formal and structured evaluation of the regulatory performance of the EAC joint assessment procedure, although some feedback has been sought through stakeholder meetings.

A recent study has been carried out among the seven active members of the EAC-MRH work sharing initiative using a similar questionnaire to the one being sent to the applicants, so that the benefit is gained from both key stakeholders.

In recent years, there has been a drive within regulatory agencies to re-engineer their processes for improved efficiency and effectiveness and this often begins with a baseline evaluation of the current process to identify strengths and weaknesses. *Effectiveness* can be defined as 'doing the right thing' often measured by the value derived by customers/stakeholders from an organisation's processes or services while *Efficiency* can be defined as 'doing things right' which saves the organization time and resources.

STUDY PARTICIPANTS

The PEER Questionnaire is being sent to applicants who have submitted marketing authorisation applications for assessment under the EAC-MRH initiative.

STUDY AIM

The aim of this study is to evaluate the effectiveness and efficiency of the current operating model of the EAC-MRH initiative including the challenges it faces as well as identifying opportunities for improvement.

STUDY OBJECTIVES

1. Obtaining the views of the applicants of the EAC-MRH initiative about the performance of the programme to date.
2. Identifying the challenges experienced by individual applicants throughout the life cycle of the EAC-MRH initiative.
3. Determining the strengths and weaknesses of the initiative
4. Identifying the ways of improving the performance of the work sharing programme.
5. Envisaging the strategy for moving forward

CONFIDENTIALITY

Thank you for agreeing to participate in this survey. **Your responses will be treated in strictest confidence and no identifiers of companies or respondents will be shared with any third party or made public**. External reports or presentations of the data will include only blinded results together with appropriate analytical interpretations.

The questionnaire is divided into five short sections and will take 20 minutes to complete. Thank you for taking time to complete it. We value your input!

E. DEMOGRAPHICS

7. Please state the name of your company _____

8. Please provide your responses to the following questions by writing your answer in the space provided or ticking the relevant box.

   a. Age: ____years

   b. Sex: ☐ Male ☐ Female

   c. Number of years of regulatory affairs experience: ____ _____years

9. State the EAC member states in which your company markets products

   ☐ Burundi

   ☐ Kenya

   ☐ Rwanda

   ☐ South Sudan

   ☐ Tanzania (Mainland)

   ☐ Tanzania (Zanzibar)

   ☐ Uganda

10. Give reasons why your company markets products in the selected member states above.

    _____

    _____

    _____

_____
_____
_____
_____
_____
_____
_____
_____

11. Give reasons why your company does not market products in the member states that have not been selected from the list above.

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

12. Do you have a separate record of applications submitted for assessment under EAC-MRH to facilitate tracking and adherence to deadlines? ☐ Yes ☐ No

F. VIEWS ON THE BENEFITS OF THE EAC-MRH INITIATIVE

Select your answers by ticking the relevant box(es)

6. In your view, what are 3 (or more) benefits of the EAC-MRH initiative to date?

☐ Leadership commitment/Governance structure

☐ Clear Operating Model

☐ Shorter timelines for approval

☐ Information sharing among regulators

☐ Building of capacity for assessments

☐ Sustainable resource base because of self-funding by countries

☐ `Harmonisation of registration requirements across the region

☐ Other (Please specify) _____

_____

7. How has the EAC-MRH initiative benefited you as applicants?

☐ Reduced burden as applicants compile one dossier (modules 2 -5) for submission to multiple countries

☐ Savings on time and resources as applicants receive the same list of questions from multiple countries enabling compilation of a single response package

☐ Shorter timelines for approval compared to that for the individual countries

☐ Access to various markets at the same time

☐ Other (Please specify) _____

____

8. How has the EAC-MRH initiative benefited <u>patients in the individual member states or in the EAC region</u>?

☐ Quicker access to quality assured medicines

☐ Reduced prices of medicines

☐ Increased availability of medicines

☒ Other (Please specify) _____

____

G. VIEWS ON CHALLENGES OF THE EAC-MRH INITIATIVE

Select your answers by ticking the relevant box(es)

2. In your view, what are 3 (or more) challenges of the <u>EAC-MRH initiative?</u>

☐ Lack of detailed information on the process for applicants

☐ Differences in regulatory performance of the countries

☐ Dependence on the countries' process for communication with applicants

☐ Lack of centralised submission and tracking

☐ Lack of ability to mandate central registration

☐ Other (please specify) _____

____

3. What are the challenges faced by <u>applicants</u> submitting applications to the EAC-MRH initiative?

☐ Differences in time to implementation of EAC-MRH recommendations by member countries.

☐ Lack of clarity about the process for submission and follow up in each country

☐ Lack of information on country websites and the EAC-MRH website about the process, milestones, timelines for pending and approved products

☐ EAC-MRH process is more stringent than individual country processes for reviews and GMP audits

☐ Differing labeling requirements in participating countries

☐ Failure by countries to adhere to promised timelines

☐ Risk of losing access to all member states once a product is rejected by EAC-MRH (i.e can no longer pursue registration in individual countries)

☐ Low motivation and appeal to use the EAC-MRH route as there are few success stories available or publicized

☐ Low motivation to use the EAC-MRH route as other review routes are now being used by individual countries e.g reliance on SRA approvals or other EAC member states are faster

☐ Other (Please specify) _____

____

4. In your view, what do you believe are the challenges faced by agencies in reviewing the EAC-MRH applications?

_____
_____
_____
_____
_____
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_____
_____
_____
_____

H. IMPROVING THE PERFORMANCE (EFFECTIVENESS AND EFFICIENCY) OF THE WORK SHARING PROGRAMME

Select your answers by ticking the relevant box(es)

Effectiveness can be defined as 'doing the right thing' often measured by the value derived by customers/stakeholders from an organisation's processes or services while *Efficiency* can be defined as 'doing things right' which saves the organization time and resources.

3. What are 3 or more ways to improve the <u>effectiveness</u> of the EAC-MRH initiative in your view?

☐ Decision-making transparency e.g., publishing Public Assessment Reports

☐ Make publicly available any information that might help applicants in managing their submissions - templates of documents, lists of Q&A, timelines and milestones, disclosure of internal SOPs, etc.

☐ Consistency in application of guidelines and decisions

☐ Use of risk-based approaches e.g., reliance pathways

☐ Engagement and interaction with stakeholders

☐ Publishing of pending products

☐ Publishing of approved products

☐ Minimising the need for country specific documents

☐ Other (Please specify) _____

____

4. What are 3 or more ways to improve the <u>efficiency</u> of the EAC-MRH initiative in your view?

☐ Specific and clear requirements made easily available to applicants

☐ Compliance with target timelines by measuring and monitoring each milestone in the review process

☐ Use of robust IT systems

☐ Transparency on metrics and statistics e.g., % completed within a timeline

☐ Improved central tracking of EAC-MRH products

☐ Improved resources e.g., number of assessors

☐ Centralised system for submission of applications and communication with applicants

☐ Other (please specify) _____

_____

5. Evaluate the performance of individual countries that you have submitted applications to for review under EAC-MRH
   Please complete only for the countries that you have submitted EAC-MRH applications to and have experience with

Measure	**Burundi**	**Kenya**	**Rwanda**	**South Sudan**	**Tanzania (Mainland)**	**Tanzania (Zanzibar)**	**Uganda**
	Yes No	**Yes No**	**Yes No**	**Yes No**	**Yes No**	**Yes No**	**Yes No**
The contact person is known	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
The process for submission of applications is clear	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
The process and timelines for EAC-MRH products are available on the website	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Communication of queries is carried out timeously (NMT 30 days after a session)	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐

E: ENVISAGING THE STRATEGY FOR MOVING FORWARD

4. Rate the following proposals to improve the current EAC-MRH operating model from 1 – 3, number 1 representing what you think would be **most effective** in improving efficiency and number 3 the **least effective**.
Enter the appropriate number in the space provided before each proposal.

☐ To continue with the current operating model unchanged.

☐ To continue with the current operating model but provide full information on the process including timelines and milestones as well as approved products on every participating country's website and on the EAC-MRH website.

☐ The establishment of a regional administrative body to centrally receive and track EAC-MRH applications which would be responsible for allocating work, apportioning the applicable fees to countries, tracking of applications and communication with applicants.

5. In your view, would the establishment of an EAC regional medicines agency, if legally possible, be the best strategy for improved performance going forward? ☐ Yes ☐ No

   Please explain why?____

   _____

   _____

6. In conclusion, what other strategies not previously highlighted can you think of that would strengthen the EAC-MRH initiative going forward?

   _____

   _____

   _____

   _____

Please feel free to use the comment box below to elaborate on any of your answers or to highlight questions and answers that you believe should have been included in this questionnaire.

Name of person completing the questionnaire: _____

_____

Title (position): _____

Date: _____

Data collection

Collection of data started in November 2021 and ended in April 2022. The questionnaire was completed by a representative responsible for EAC joint procedure submissions in each company.

RESULTS

For the purpose of clarity, the results are presented in five parts: Demographics; Benefits of the EAC-MRH initiative; Challenges of the EAC-MRH initiative; Improving the performance (effectiveness and efficiency) of the work-sharing programme; and envisaging the strategy for moving forward.

Part I- Demographics

Most respondents, who presented the views of their companies, held roles as head of regulatory affairs in their respective companies, with regulatory experience ranging between 5 and 21 years. The companies that participated in the study were classified according to their product portfolio and location of their manufacturing sites. Eight (58%) were foreign generic pharmaceutical companies, three (21%) were local manufacturers of generics and three (21%) were innovator pharmaceutical companies (Figure 6.2). Of the 144 dossiers/ applications assessed as of 31 December 2021, 55% were generics submitted by foreign companies, 22% were new active substances submitted by innovator companies and 23% were generics submitted by the local company.

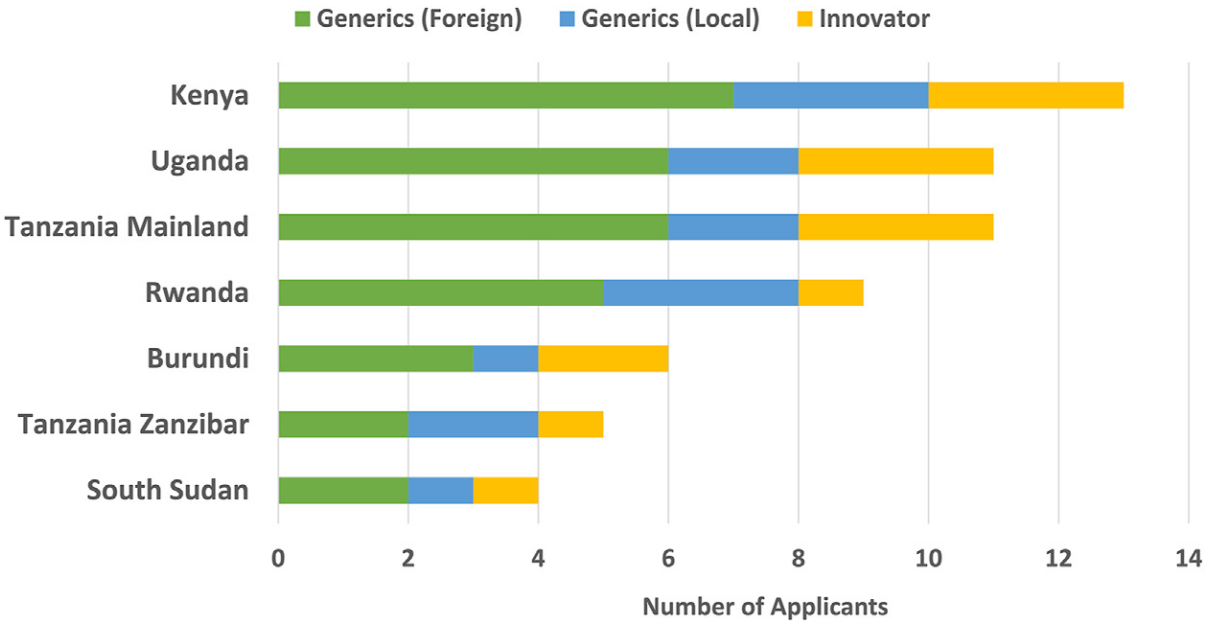
The EAC countries in which companies market their products.

All the companies indicated they had a separate record of applications submitted for assessment under EAC-MRH to facilitate tracking and adherence to deadlines. The majority of the companies market products in Kenya, Tanzania Mainland and Uganda (Figure 6.2). The applicants gave various reasons why their companies market products in the selected countries, including the fact that these countries provide excellent and ready market potential for pharmaceutical companies, as wider market coverage maximises revenues and economies of scale. In addition, there is an available patient pool for products in these markets, with market

stability and predictability, with an established distribution chain, as well as mature healthcare systems.

Most companies are interested in registering medicines in countries with developed medical systems like oncology and rheumatology centres. The majority of pharmaceutical companies want to ensure maximum reach and access of essential healthcare products to positively impact society and sometimes the marketing of products in these countries is based on partner and donor interest. Companies that are leading manufacturers of essential medicines for high disease burden like antiretrovirals and anti-malarials in the region are marketing medicines and healthcare solutions not only in the EAC member countries, but in the whole of Sub-Saharan Africa. The capacity of NMRAs in the region is key, as some of the countries have not initiated the process of medicine registration as they do not have fully functional regulatory authorities. Some countries access some medical products through import permits so that marketing in such countries is not required. Aspects such as lack of security, political, and market stability, weak regulatory and healthcare systems, weaknesses in the supply and distribution processes are some reasons why some manufacturing companies do not market products in all EAC countries.

Figure 6.2 EAC Partner States where companies market products



Part II- Benefits of the EAC-MRH Initiative to Regulators and Pharmaceutical Companies

Pharmaceutical companies identified the harmonisation of registration requirements across the region, shorter timelines for approval and information sharing among regulators as well as building capacity for assessments as the top four benefits of the EAC initiative (Figure 6.3). One registration for all countries was also mentioned as a benefit, leading to access to various markets at the same time. However, it was noted that the shorter approval and clear operating model are currently applicable only for Tanzania.

Several benefits of the initiative were indicated, including reduced burden, as applicants compile one dossier (modules 2–5) for submission to multiple countries, savings in time and resources as applicants receive the same list of questions from

multiple countries, which enables the compilation of a single response package. Shorter timelines for approval compared with those for individual countries as well the ability to launch products simultaneously in all markets were also identified (Figure 6.3)

Figure 6.3 Benefits of the EAC-MRH initiative - To Regulators

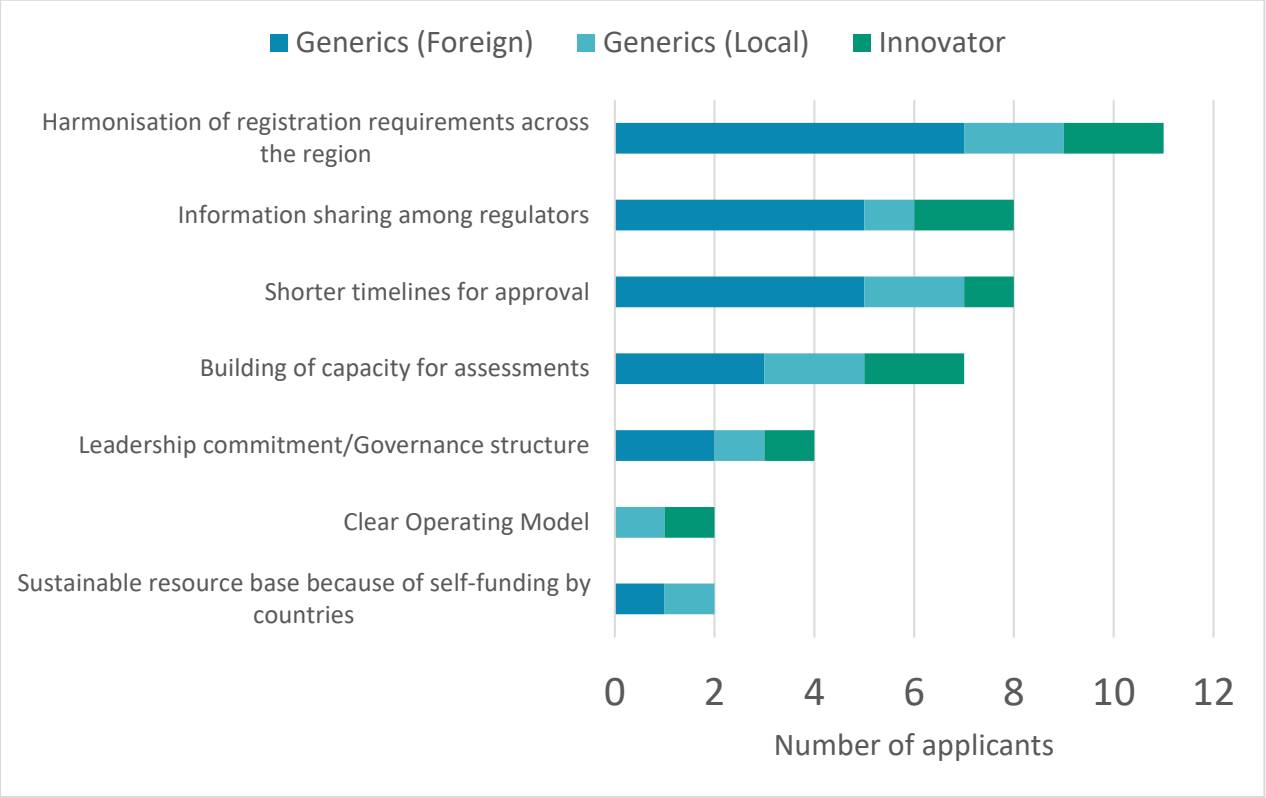
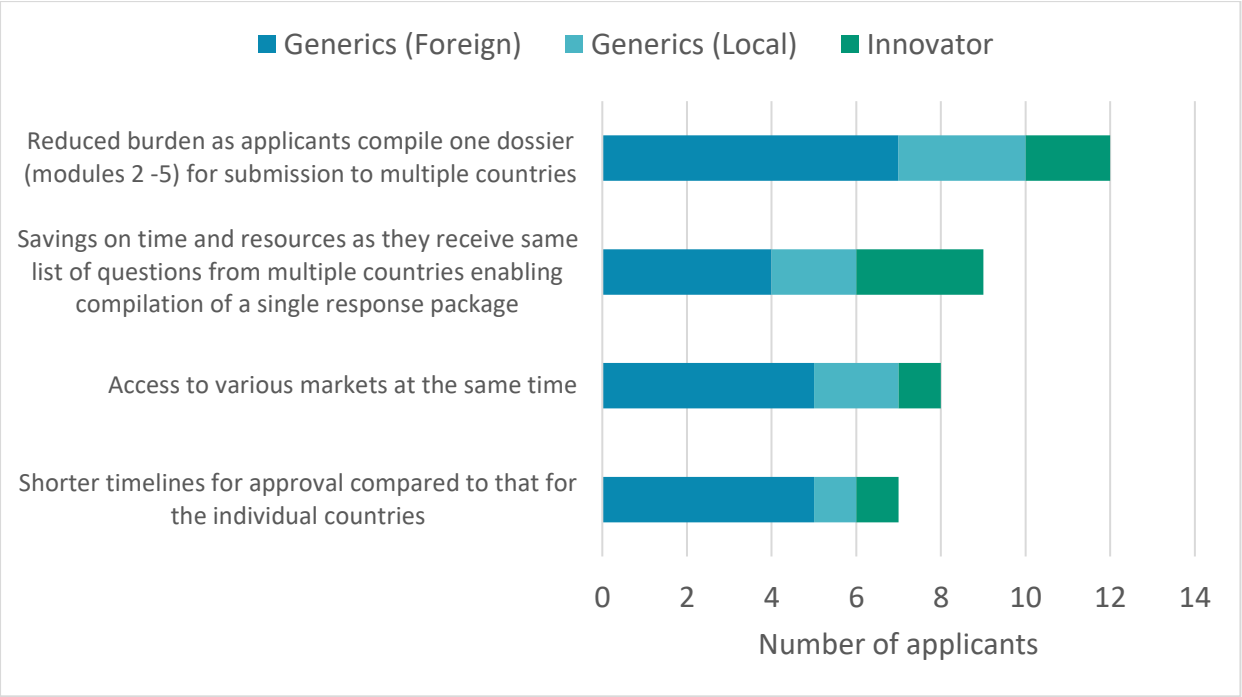


Figure 6.4: Benefits of the EAC-MRH initiative -To Applicants



However, some companies mentioned that they submitted documentation for EAC in August 2019 but did not receive any response from the EAC-MRH Secretariat. Meanwhile, they obtained a national registration for their products based on normal assessment procedure in three countries (Tanzania, Uganda and Kenya). As previously mentioned, others indicated that some of the above benefits are currently. applicable only for Tanzania, as the procedure's benefits declined over time for other countries since an EAC positive opinion does not directly result in approval in those countries. Also, NMRAs often request additional information after an EAC positive opinion, which further delays approval and patients' access in individual markets.

The applicants are required to apply for a marketing authorization in EAC countries after a joint positive recommendation. However, the time to registration of the product at a country level will depend on when the country specific application is submitted and if additional information is requested by the country. Therefore, the times given for approval represent the time to national approval and not to the time of EAC recommendation. In general, full applications are submitted with only a few abridged dossiers. Most of these applications are for generic products where only quality assessments are conducted. Furthermore, the

assessment reports are only from the EAC region. Unfortunately, according to some applicants, their interaction with the EAC procedure has not led to any improvement in product dossier assessment, although their hope is that in the future dossier submission will improve. Quicker access to quality-assured medicines and increased availability of medicines were the benefits for patients indicated by all applicants, although reduced prices of medicines is not yet an outcome of the initiative for patients.

Part III- Challenges of the EAC-MRH Initiative

Some of the challenges of the EAC-MRH initiative highlighted were a lack of detailed information on the process for applicants, differences in regulatory performance of the countries, a dependence on the countries' process for communication with applicants; a lack of centralised submission and tracking processes; an inability to mandate central registration; and an unclear process for obtaining actual marketing authorisation after assessment (Figure 6.4). Other challenges include the lack of harmonisation between the different EAC member states or harmonisation for variation processes. There is a lack of uniformed and binding requirements for all countries as, although regional guidelines exist, they are not always fully implemented in the national procedures. Also, the presence of country-specific requirements that follow an EAC-MRH positive opinion further delays the approval process.

Challenges faced by applicants making a submission to the EAC-MRH initiative

The top three challenges faced by applicants in making a submission to the EAC-MRH initiative were the lack of information on individual country or EAC websites about the submission process, milestones or timelines or a listing of pending and approved products (Figure 6.4). Further challenges include a lack of clarity about the process for submission and follow-up in each country, and the failure by countries to adhere to promised timelines.

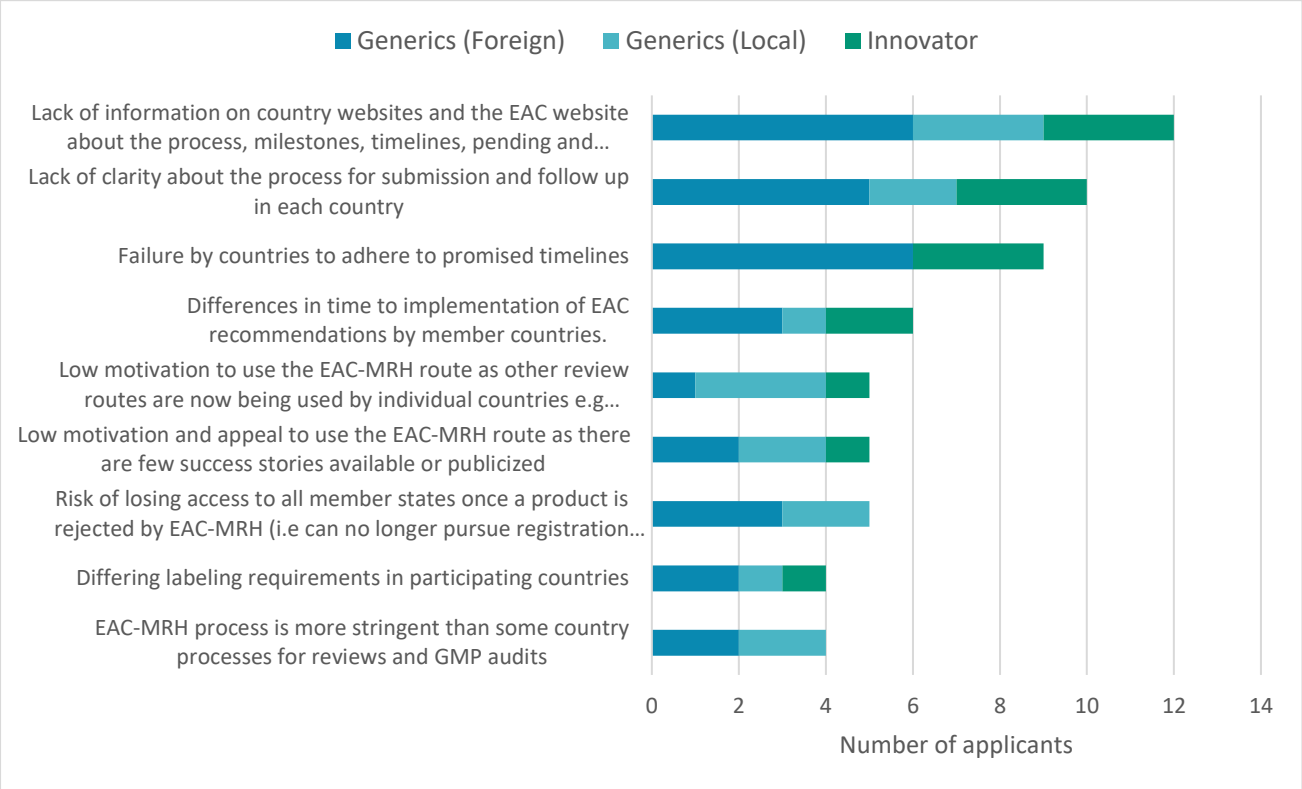
Other challenges faced by pharmaceutical companies were the differences in time to the implementation of EAC recommendations by member countries; the risk of losing access to all member countries once a product is rejected by EAC-MRH as applicants can no longer pursue registration in individual countries and the need to update online submission and tracking by the applicant.

Challenges faced by authorities in reviewing the EAC-MRH applications.

Pharmaceutical companies stated several challenges faced by NMRAs in reviewing the EAC-MRH applications. It was claimed that the EAC-MRH requirements are more numerous and stringent as compared with those of individual countries, so companies need to provide all query details received from EAC. There are different levels of buy-in from individual countries and differing application requirements in some countries; for example, labelling requirements and some medicines are accepted in some countries but not others. The lack of legal/ regulatory binding requirements in the national regulations is also a critical challenge and whilst some regional guidelines exist, they are not always fully implemented in the national regulations (Figure 6.5).

Figure 6.5 Challenges of the EAC-MRH initiative.

To Applicants

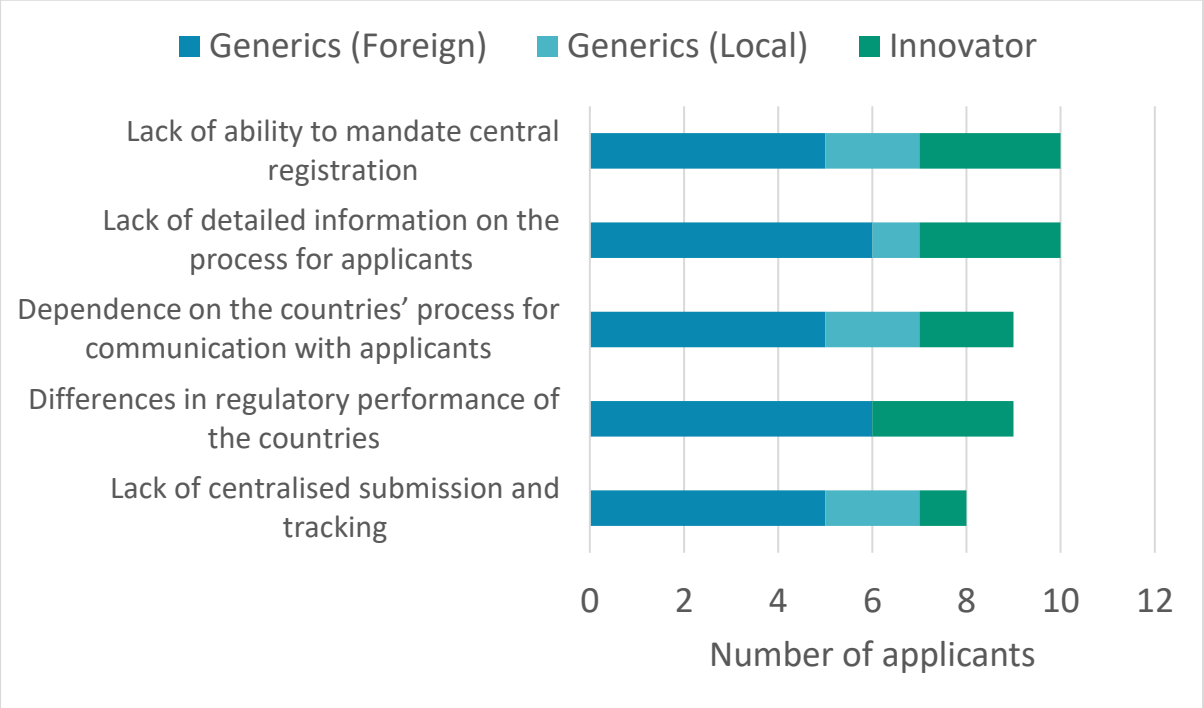


Another challenge is the lack of structured mechanisms for the execution of the joint assessment procedures, and limited capacity delays convening assessment meetings and eventually approvals. There are several logistical constraints including the lack of clear

mandate between authorities and the EAC-MRH Secretariat, a lack of a permanent joint Secretariat and shared calendar that include NMRA schedules. Furthermore, the dependence on a single individual with sole responsibility for process at each authority is a key challenge. The coordination for good manufacturing process (GMP) inspections, including desk reviews and the sharing of information between countries was also mentioned as a challenge. The pharmaceutical companies commented that the lack of sustainable resources and funds dedicated to EAC-MRH affects the availability of assessors and the prioritisation of EAC-MRH assessment over national activities (Figure 6.5).

Figure 6.6

To Regulators Challenges of the EAC-MRH initiative.



There is also a constraint in the flow of information among the active NMRAs who participate in the evaluation process, leading to a delay in adopting the recommendations from the outcome of the evaluation process by countries.

Part IV- Improving Performance (Effectiveness and Efficiency) of the EAC Initiative

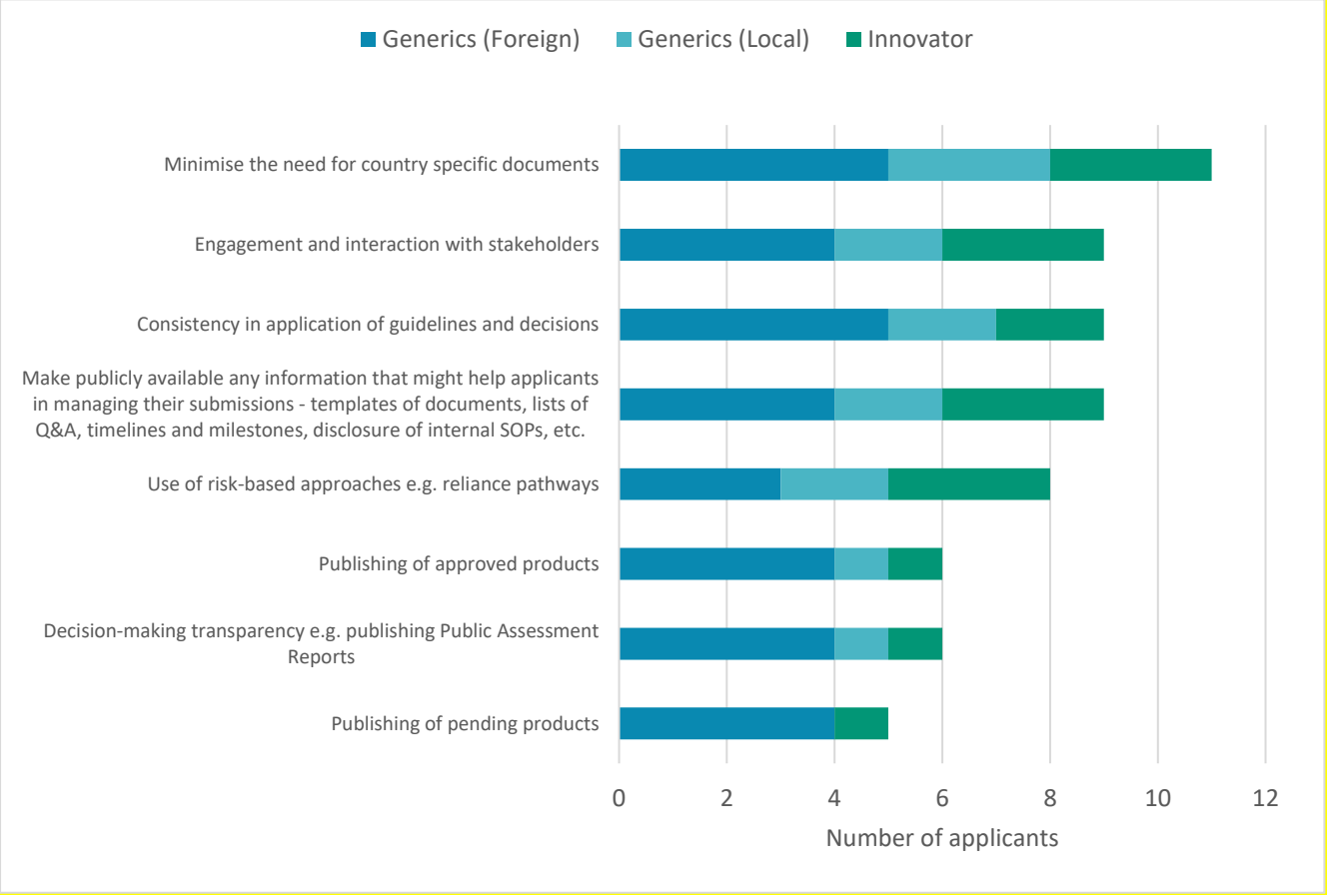
A number of ways to improve the effectiveness of the EAC initiative were mentioned, which include minimising the need for country-specific documents, engagement and interaction with stakeholders, making publicly available any information that might help applicants in managing their submissions such as document templates, lists of questions and answers,

timelines and milestones, disclosure of internal standard operating procedures, consistency in application of guidelines and decisions and the use of risk-based approaches such as reliance pathways were identified by the majority of applicants as ways to improve effectiveness (Figure 6.6).

Improving efficiency of the EAC-MRH initiative

Most applicants indicated that improving efficiency of the initiative would entail compliance with target timelines by measuring and monitoring each milestone in the review process (Figure 6.7). It would also include a centralised system for submission of applications and communication with applicants, improved central tracking of EAC products as well as specific and clear requirements made easily available to pharmaceutical companies. An appropriate regulatory framework that recognises and gives appropriate recognition and resources to regional procedures in national regulations would also be invaluable.

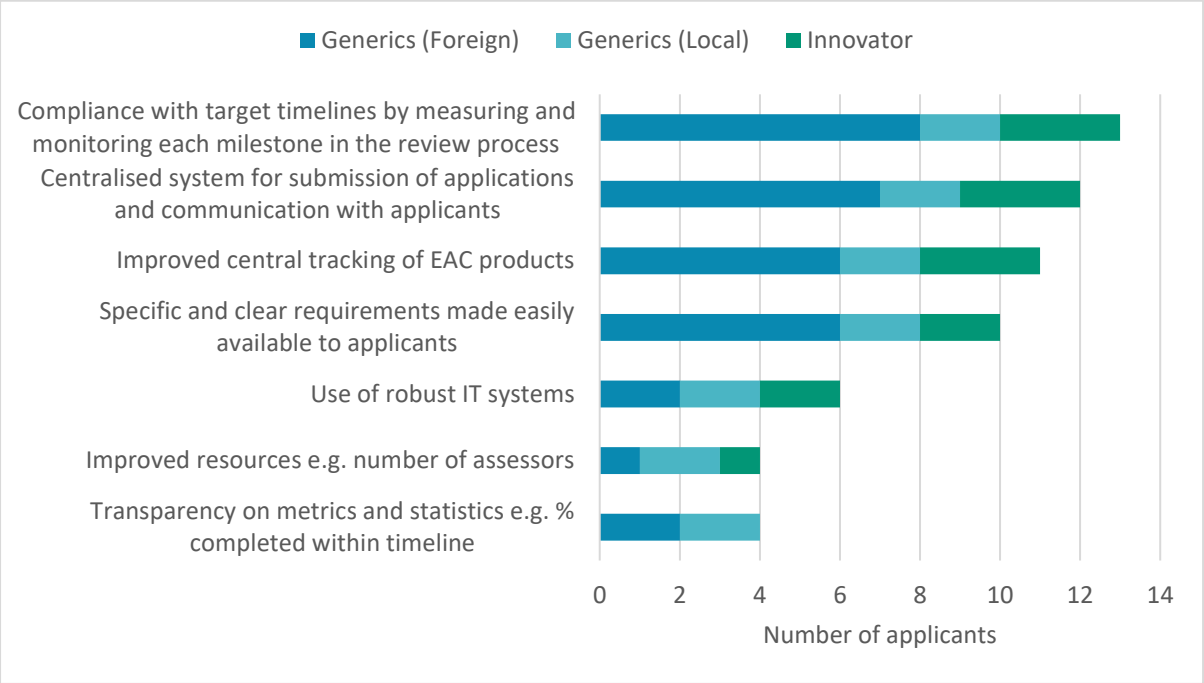
Figure 6.7 Ways to improve the effectiveness of the EAC initiative.



Part V – Strategies for Improving the Current EAC-MRH Operating Model

The main proposal made by the pharmaceutical companies to improve the EAC operating model is the establishment of a regional administrative body to centrally receive and track EAC applications. This approach would include being responsible for allocating work, apportioning the applicable fees to countries, tracking of applications and communication with applicants. The majority of the pharmaceutical companies were also of the view that the establishment of a Regional Medicines Authority in the EAC, if legally possible, would be the best strategy for improved performance.

Figure 6.8 Ways to improve the efficiency of the EAC initiative.



Part VI – Envisiging the Strategies for Moving Forward

Several reasons were given as to the importance, benefits and strengths of a regional authority and these included an established EAC centre with representatives/staff, which would avoid delays in the assessment process since the evaluation committee will be fully fledged instead of evaluators having to convene from various countries and/or regions. This would harmonise the registration process in the EAC partner states, leading to a less expensive and faster

registration procedure. A regional authority would also improve access to medicines as it will enhance other interrelated aspects like the movement of goods, customs requirements as well as having just a license for the product may not be sufficiently efficient to assure product access.

Furthermore, a centralised review with legal responsibility to share reviews, documents, and activities between countries and the industry would minimise overlapping requests for inspections and information sharing. Centralising the evaluation process would increase the efficiency and effectiveness and make communication between stakeholders easier and clearer especially if there are dedicated personnel working in the regional medicines' authority. Applicants would know exactly who to call and interact with regarding their submissions as the employees would only be involved with EAC applications and not applications from individual countries. Applicants also indicated that a regional authority would influence the development of an online portal for submission and tracking of the application status for the sponsors and also enable a faster and easier approval process with minimum requirements. The ease of verifying information centrally received for EAC-MRH applications would facilitate the tracking of applications and subsequent communication with the pharmaceutical companies.

However, some pharmaceutical companies were of the view that the establishment of a Regional Medicines Authority might not be a good strategy moving forward, especially if it encounters sustainability challenges where the authority has a higher workload and is underfunded. Another proposal was that with the ongoing activities by the African Union toward the operationalisation of the African Medicines Agency (AMA), there is now no additional need for duplication of regulatory processes with protracted lobbying times across the regions. The best approach would be to facilitate ongoing regional harmonisation frameworks and set the stage for a single Pan-African Agency (AMA). It is important to first clarify the EAC-MRH process, and the role of each individual NMRA, then to fully implement regional procedures in the national authorities. Adding a regional authority without solving the current challenges, would add to the complexity, especially considering that the continental authority (AMA) will soon be fully established. It would also become difficult for applicants to navigate between national, regional and continental institutions, as well as between

numerous available registration pathways. Moreover, the challenge of lifecycle management, including post approval changes submission/approval and license maintenance is still only foreseen by national procedures.

DISCUSSION

The aim of this study was to evaluate the effectiveness and efficiency of the current operating model of the EAC-MRH initiative from the applicants' perspective and to identify the challenges it faces as well as opportunities for improvement. Pharmaceutical companies affirmed the importance and relevance of the EACMRH work-sharing initiative, as it has benefitted regulators, applicants and patients in the region. As the first region to implement medicines regulatory harmonisation in Africa, the EAC has made major strides toward achieving its main objective of improving patients' access to high-quality medicines in the region. The EAC-MRH initiative has made the process of registration and marketing authorisation more efficient to pharmaceutical companies through the use of harmonised technical standards and optimisation of regulatory requirements, thereby resulting in the reduction of timelines for review of applications (Mashingia et al., 2020; Ndomondo-Sigonda et al., 2020).

Comparing the views of applicants in this study with those of regulators Ngum et al. (2022), identified similar challenges. These included the lack of a centralised submission and tracking process for the work-sharing initiative entailing a lack of clarity about the process for submission and follow-up in each country for applicants. In addition, a lack of ability to mandate central registration has led to a failure by countries to adhere to promised timelines. The regional guidelines that exist are not fully implemented in all the countries. Furthermore, the unclear process for obtaining actual marketing authorisation after assessment through the initiative has caused various levels of company buy-in for the differing application requirements from individual countries. This delay by countries in issuing the actual market authorisation to applicants was affirmed in another study conducted in 2019 by Dansie and associates. The negative effect of the lack of information on individual country and EAC websites cannot be overemphasised and communication from the EAC Secretariat has also been lacking.

Moreover, due to limited capacity and resources, there is a weak coordination mechanism and the lack of structured mechanisms for the execution of the joint assessment procedures. This

has led to the dependence of the initiative on the countries' processes for communication with pharmaceutical companies and insufficient engagement between applicants/ manufacturers and stakeholders. Finally, as reported by Dansie and others in 2019, the EAC-MRH initiative has not motivated increased company interest in country markets that are less attractive because of political or logistic issues.

As a result of this study, it is recommended that there should be both effective communication and engagement by the industry with the agencies and coordinators should be empowered to talk directly with applicants. There should also be transparency in communication as well as adequate inclusion of all stakeholders, with the industry as a key user of the procedures in the relevant discussions. There should be predictability of processes and adherence to timelines and procedure. There is a need for a holistic approach for the EAC-MRH procedure in terms of eligible product categories and the inclusion of lifecycle management activities. Company study participants also suggested that financial incentives be given to applicants to follow the joint evaluation pathway; that is, fees for joint assessment should be lower when compared with those for single country assessment.

Adherence to the EAC-MRH process by the NMRAs should be promoted. Arik and others also recommended a cooperation framework agreement between NMRAs and the EAC (2020). Instituting a legally binding framework would enhance implementation of joint decisions (Giaquinto et al., 2020) and one of the study participants further suggested the elimination of national assessments of dossiers.

RECOMMENDATIONS

The following are some key recommendations listed below in order of implementation priority to improve the effectiveness and efficiency of the EAC-MRH initiative.

1. There is a need for engagement with the industry with a clear registration procedure for the EAC-MRH process. Clear guidance needs to be implemented based on established harmonised regulations and procedures across the whole region and adhered to at the national level.
2. The EAC Secretariat should closely track national marketing authorisations and GMP assessments after a positive joint assessment to ensure that each country implements the registration within an appropriate timeframe.

3. A study should be conducted to understand why the benefits of the work-sharing initiative have deteriorated over time in some countries and why an EAC positive opinion does not directly transform to individual country approvals.
4. Financial incentives should be given to applicants to follow the joint evaluation pathways with the fees per country being lower for joint assessments compared with those for single country assessment.
5. Stronger mutual recognition is needed between member countries.
6. The establishment of an EAC Regional Medicines Authority would be the best strategy for improved performance.

CONCLUSIONS

While harmonisation is key to ensuring access to safe, effective and high-quality medicines, there are also other elements of the healthcare system such as accessibility and affordability that need to be in place in order to realise the full benefits of the medicines regulatory harmonisation initiative. It is imperative for the recommendations made in this study to be fully implemented to ensure faster registration of the much needed essential medicines by patients in the EAC region. Full implementation of the EAC road map 2020–2022 is critical to address some of the immediate issues. It is worth noting that Rwanda, one of the EAC member countries, will be hosting the African Medicines Agency and with the combined efforts by the African Union Partners to strengthen regulatory systems on the continent, the operationalisation of AMA would strengthen the EAC-MRH initiative.

SUMMARY

- The focus of this study was to evaluate the effectiveness and efficiency of the current operating model of the EAC-MRH initiative from the applicants' perspective, including the challenges it faces as well as to identify opportunities for improvement.

- A questionnaire, Process Effectiveness and Efficiency Rating for Industry (PEER-IND) was developed specifically for this study and completed by those pharmaceutical companies who had submitted their applications to the EAC-MRH between 2015 and 2021.

- Several benefits of the initiative included a reduced burden for applicants as they compile one dossier (modules 2–5) for submission to multiple countries, as well as savings in time and resources as applicants receive the same list of questions from multiple countries, shorter timelines for approval compared with those for individual countries as well the ability to launch products simultaneously in all markets.

- Key challenges faced by applicants in making a submission to the EAC-MRH initiative included a lack of information on individual country or EAC websites about the submission process, milestones, timelines or a listing of pending and approved products, a lack of clarity about the process for submission and follow-up in each country, and the failure by countries to adhere to promised timelines.

- The main proposal made by the pharmaceutical companies to improve the EAC operating model is the establishment of a regional administrative body to centrally receive and track EAC applications. This approach would include being responsible for allocating work, apportioning the applicable fees to countries, the tracking of applications as well as communication with applicants.

CHAPTER 7

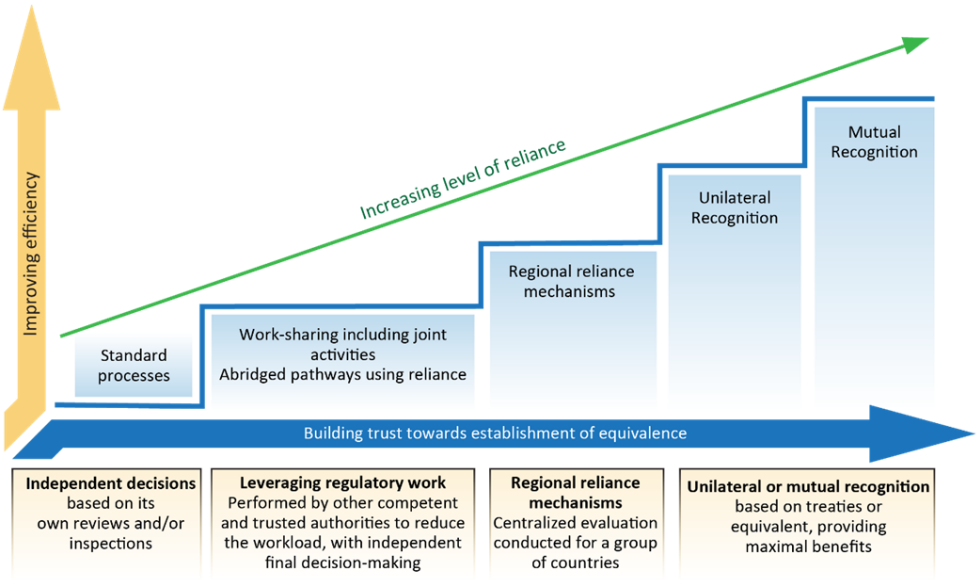
COMPARISON OF THREE REGIONAL MEDICINES REGULATORY HARMONISATION INITIATIVES IN AFRICA: EAC-MRH, ZAZIBONA AND WA-MRH INITIATIVES

INTRODUCTION

It is the responsibility of national medicines regulatory authorities (NMRAs) to ensure that medical products such as medicines and vaccines used by the public are of good quality, safe and effective (Rago et al, 2008). The role of NMRAs was brought into the spotlight during the COVID-19 pandemic, as these agencies were responsible for the review and approval of novel vaccines in the shortest possible time. This public health emergency resulted in an increase in the use of reliance and collaborative registration pathways among regulatory authorities, as they sought to shorten the time to market various life-saving medical products (EMA, 2024).

Reliance is defined by the World Health Organization (WHO) as "the act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, in reaching its own decision" (Figure 7.1) (WHO, 2021a & WHO, 2021b). The foundation for NMRA use of reliance was built prior to the COVID-19 pandemic, when NMRAs invested in implementing reliance principles to improve efficiency and establish the relevant systems in accordance with the WHO good reliance practices guidelines (WHO, 2021a & McAuslane et al, 2023). A type of reliance is joint review or work sharing, in which the review or assessment of a medicine is conducted by two or more NMRAs collaboratively. Examples of joint review or work-sharing initiatives are the East African Community Medicines Regulatory Harmonisation (EAC-MRH) initiative, the ZaZiBoNa/Southern African Development Community Medicines Regulatory Harmonisation (SADC MRH) initiative and the Economic Community of West African States Medicines Regulatory Harmonisation (ECOWAS-MRH) initiative currently implemented in Africa through the African Medicines Regulatory Harmonisation Initiative (AMRH) established in 2009 (Ndomondo-Sigonda et al, 2018).

Figure 7.1 Key concepts and levels of reliance (WHO, 2021b).



Whilst individual NMRAs in Africa can review products independently, there are currently five major regional initiatives that were designed to bring groups of NMRAs together, in order to expedite patients' access to medicines and make recommendations for registration to the individual NMRAs. However, an NMRA can be involved in more than one regional initiative due to their geographical position. The three major regional initiatives in Africa are ZaZiBoNa, the EAC-MRH and the ECOWAS-MRH, which have been evaluated and compared. In these regions, because there is not an established legal framework, the recommendations are not mandated as would be the situation for a centralised procedure. Neither is there mutual recognition, which would be the situation with a decentralised procedure, as is exemplified in the European Medicines Agency (EMA).

The East African Community Medicines Registration Harmonisation initiative

The EAC MRH initiative was established in 2012 as a 5-year pilot and the first regulatory harmonisation project under the AMRH, with the overarching goal to improve access to quality medicines and to test the feasibility of regulatory harmonisation in Africa (Sillo et al, 2020). Participating countries were Burundi, Kenya, Rwanda, South Sudan, Tanzania and Uganda (Ngum et al, 2022). The beginning model employed by the EAC involved NMRA staff from

participating countries travelling to Copenhagen to participate in joint assessment sessions with the WHO Prequalification of Medicines (PQ) programme (Sillo et al, 2020). However, this model was later discontinued due to unsustainability and assessment sessions are now held within the EAC region. In the current model employed by the EAC, lead NMRAs are designated for key functions: Tanzania for medicines evaluation and registration, Uganda for good manufacturing practices (GMP) inspections, Rwanda for information management systems and Kenya for quality management systems (Sillo et al, 2020). Therefore, products are submitted to the Tanzania NMRA, which conducts the validation and primary review of the application before presenting it to the joint assessment session, which is attended by a representative from each country for further consideration. Only after a recommendation is issued, will the applicant be expected to submit individual applications for marketing authorisation and a fee to each NMRA (Ngum et al, 2022). Marketing authorisations are granted individually by each country.

The Tanzania NMRA was the first in Africa to attain maturity level 3 status in the WHO Global Benchmarking Tool (GBT) programme in 2018 (WHO, 2021b). Maturity level 3 indicates a stable and well-functioning regulatory system (WHO, 2019).

ZaZiBoNa / Southern African Development Community Medicines Regulatory Harmonisation initiative

ZaZiBoNa was founded in 2013 by Zambia, Zimbabwe, Botswana and Namibia to address the challenges of long registration times and inadequate capacity and resources in these countries.[10] In 2015, the SADC MRH project was launched, absorbing ZaZiBoNa. Membership has since grown to include all 16 SADC countries (9 active members, 5 non-active members and 2 observers). Active member status is determined by the capacity to conduct assessments and GMP inspections and the active member countries are Botswana, Democratic Republic of Congo, Malawi, Mozambique, Namibia, South Africa, Tanzania, Zambia and Zimbabwe (Sithole et al, 2020). The SADC MRH initiative does not have centralised submissions or approvals/registrations due to the absence of a regional legal framework. In the current model, applicants simultaneously submit applications for registration and pay fees to each of the countries in which they wish to market their medicinal products (Ndomondo-Sigonda et al 2018 & Sithole et al, 2020). To be eligible for joint assessment, applications should be

submitted to a minimum of two countries. The assessment of dossiers/applications is carried out using a rapporteur and co-rapporteur before consideration of the report by a group of assessors from all the active member countries. Once the evaluation is concluded, an assessment report with a recommendation and a consolidated list of questions is produced and communication of the list of questions to the applicants as well as the final decision on the registration/marketing authorisation of the medicinal products is left to the individual participating countries (Sithole et al, 2020). Two SADC MRH NMRAs have attained WHO GBT maturity level 3 status, Tanzania, as previously mentioned, and South Africa in 2022 (WHO, 2018 & WHO, 2022).

Economic Community of West African States Medicines Regulatory Harmonization Initiative

Similar to other regions in Africa, the ECOWAS region faced challenges in technical capacity and financial resources. In addition, because the ECOWAS region comprises Portuguese-, English- and French-speaking countries (Daniel, 2024), the differences in official national language further complicated and delayed the implementation of harmonisation. The ECOWAS MRH initiative was launched in 2017 by the West African Health Organization (WAHO) to improve the availability of high-quality, safe and effective medicines and vaccines in ECOWAS (Owusu-Asante et al, 2022). The ECOWAS MRH initiative aimed to reduce the time to registration and improve regulatory oversight through jointly registering locally manufactured and imported medical products (Daniel, 2024). Although the ECOWAS MRH initiative was launched in 2017, joint assessments commenced in 2019 and to date, seven NMRAs; that is, Burkina Faso, Cote d'Ivoire, Ghana, Nigeria, Senegal, Sierra Leone and Togo have participated in the sessions. Although these seven countries participate in the joint assessments, the outcomes are taken as a basis for the regulatory decision in all 15 NMRAs in the ECOWAS region (Owusu-Asante et al, 2022). In the model employed by the ECOWAS MRH, a country is appointed to serve as lead NMRA/coordinator for two years on a rotational basis. This lead NMRA is assigned to serve as coordinating agency for product applications and is responsible for receiving, validating, and preparing applications for review by an assessment team comprising staff from the seven participating NMRAs. The report is then considered during the joint assessment session of the expert working group. The WAHO

Secretariat serves as an administrative agency responsible for issuing notifications of recommendations at the regional level. Once this process is completed, each NMRA that receives an application for a jointly reviewed product implements their national procedure to issue a national marketing authorisation. Applicants are given a maximum of two years after the regional review to submit applications for marketing authorisation to countries of their choice. Two ECOWAS NMRAs attained WHO GBT maturity level 3 status Ghana in 2020 and Nigeria in 2022 (WHO, 2022 & ECOWAS, 2019).

A common challenge for all three regions implementing harmonisation initiatives was the varying regulatory capacities of participating countries. Barton and colleagues (2019) suggested three factors that may be more important: "(1) fragmented and complex drug regulations, (2) suboptimal enforcement of existing regulations, and (3) poorly designed disincentives for non-compliance." To address this issue, capacity building was included in the regional activities to improve standards, build trust and facilitate the proposed harmonisation and reliance initiatives. The AMRH was posited as a precursor to the AMA, which is in the process of being operationalised as a specialised agency of the African Union (AU) to improve access to high-quality, safe and efficacious medical products in Africa (Ngum et al, 2023). It is therefore timely and necessary to conduct a comparison of the existing regional harmonisation initiatives to identify opportunities for improvement and alignment.

STUDY OBJECTIVES

1. Compare the operating model, review process and requirements of the three harmonisation initiatives
2. Compare the successes and challenges of the initiatives
3. Identify opportunities for improvement and alignment of the initiatives and develop recommendations for the way forward

METHODS

Study participants

All seven members of the EAC MRH (Burundi, Kenya, Rwanda, South Sudan, Tanzania, Uganda and Zanzibar) as well as all nine active members of the ZaZiBoNa/SADC MRH (Botswana, Democratic Republic of Congo, Malawi, Mozambique, Namibia, South Africa,

Tanzania, Zambia and Zimbabwe) and all seven members of the ECOWAS MRH (Burkina Faso, Cote d'Ivoire, Ghana, Nigeria, Senegal, Sierra Leone and Togo) participated in the three initiatives that were used for this comparative study. Each regulatory authority was asked to nominate one individual for completing the questionnaire, who had the responsibility for monitoring and documenting regulatory performance metrics.

Content validity of the PEER Questionnaire

Data were collected in 2021 and 2022 using the Process, Effectiveness and Efficiency Rating questionnaire (PEER) developed by the authors. In order to further ascertain the content validity of the PEER questionnaire the respondents were asked to answer seven questions with a "yes or no" response options following completion of the PEER questionnaire (Supplementary Box1): Did you find the questions clear and straightforward to respond?; Did you find the response options relevant to the heading of each section (A to E)?; Did you find the questions relevant to the aims and objectives of the study?; Did you find the questions relevant to your authority and work-sharing initiative?; Did you find any relevant questions missing? If yes, please state which questions were missing in the space provided after this list of questions; Did you find any questions that should be excluded? If yes, please state the questions that should be excluded in the space after this list of questions; Did you find the questionnaire useful to reflect on both your agency experience as well that of the initiative?

In addition, as part of the cognitive debriefing aspect of the content validity and triangulation of the responses to the PEER questionnaire, semi-structured interviews were carried out with the original survey respondents, and this was designed specifically in order to fulfil the trustworthiness criteria such as credibility, confirmability, dependability and transferability by clarifying respondents' answers and confirming that they had fully understood the questions and their answers.

Furthermore, the rigour and quality of the qualitative part of our study was tested including: credibility, through close and maintained engagement with the respondents (i.e., focal person) and triangulation; confirmability, through involving the head of each authority by checking the responses of the "focal person" and the research and keeping notes of the course of events; dependability, through keeping written accounts of the qualitative research process; and

transferability, through detailed and comprehensive step-by-step description of the structure and procedure and their operationalisation to clarify certain answers and confirm that the respondents had fully understood the questions and their answers (Adler, 2022, Gunawan 2015 & Haq et al, 2023).

Data collection

The PEER questionnaire was completed by the focal person/assessor in each country and validated by the head of the authority. The questionnaire comprised five sections under the headings *Demographics*; *Benefits*; *Challenges*; *Improving the performance (effectiveness and efficiency) of the work-sharing programme;* and *Envisaging the strategy for moving forward*. Data were also extracted from the literature.

Based on the synthesis of the results, it was hoped that the author would generate a series of recommendations, which would then be presented to the regulatory agencies for their endorsement.

The PEER questionnaire was developed and validated by the author in association with the regulatory authorities specifically for this study. It was piloted with two regulatory authorities in each of three regions who were given the opportunity to comment on the content and the relevance of the questionnaire using a 7-item checklist (Supplementary Box1). As part of the relevance aspect of their evaluation they were asked to comment on what was missing and what should be deleted (as not relevant) from the questionnaire. As a result, minor changes were implemented and the final version of the PEER questionnaire was constructed. The study participants were then given two weeks to complete the questionnaire, and two reminders were sent out subsequently so that the data from all participating regulatory authorities were completed within the month after initiation. It was suggested that the questionnaire, which was sent out to the participants by e-mail, could be completed in 15 minutes (average time taken to complete during the pilot) and returned by e-mail as an attachment. Furthermore, a triangulation approach was used in this study, employing multiple methods of data generation including online Zoom virtual interviews in order to ascertain the accuracy of the study participants' responses as well as to develop a comprehensive understanding of the phenomena being explored.

Data processing and analysis

The study was exploratory (hypothesis generating) and the nature of the data generated through the PEER questionnaire and the interviews (which were transcribed verbatim) was qualitative. The content analysis technique was used to analyse the qualitative (text) data. The content analysis of the qualitative data employed a conventional approach, using inductive coding based on the data, from which a set of cohesive themes were then generated.

An initial meeting was conducted to examine the content of the data collected and identify initial concepts across the different forms of data collected. Data in the form of key phrases, statements, lists, were independently extracted from the PEER Questionnaire and transcribed texts. A thematic analysis was undertaken where the researcher got familiar with different forms of data and added initial codes (Howitt, 2008). Constant comparison across the different forms of data informed an initial thematic framework to enable consistent coding of the data. If themes were identified from the data that did not fit the initial coding framework, a new code was established to involve the theme in the analysis (Howitt, 2008). Reliability was therefore established through discussion, and findings were based on researcher agreement Charmaz, 2006 & Spencer et al, 2014). Descriptive statistics such as frequency were used to analyse the nominal data.

RESULTS

Study Participants Characteristics and Response Rate

Each regulatory authority nominated a focal person who was responsible for measuring and monitoring regulatory performance of their respective region. Each focal person from the seven members of the EAC MRH (Burundi, Kenya, Rwanda, South Sudan, Tanzania, Uganda and Zanzibar) as well as all nine active members of the ZaZiBoNa/SADC MRH (Botswana, Democratic Republic of Congo, Malawi, Mozambique, Namibia, South Africa, Tanzania, Zambia and Zimbabwe) and all seven members of the ECOWAS MRH (Burkina Faso, Cote d'Ivoire, Ghana, Nigeria, Senegal, Sierra Leone and Togo) completed the PEER questionnaire and took part in the interview, resulting in a 100% (i.e., 23 respondents) response from each of the regions.

Part I: Requirements and review process

A comparison of the three harmonisation initiatives was conducted (Table 7.1).

Table 7.1 Comparison of the review process and requirements for MRH of the EAC, ZaZiBoNa/SADC and ECOWAS initiatives

	EAC- MRH	**SADC MRH / ZaZiBoNa**	**ECOWAS MRH**
Type of procedure	Decentralised; however, there is no flexibility in selection of lead NMRA which is the equivalent of the Reference Member State and the EAC Secretariat serves as an administrative agency	Hybrid of decentralised and centralised; implementing NMRA serves as a coordinating agency	Hybrid of centralised and decentralised procedure; WAHO Secretariat serves as an administrative agency and the lead NMRA serves as coordinating agency
Legally binding framework	None	None	None
Eligibility criteria for joint review	Previous intention to market in all participating countries, currently minimum of 2 countries	Submission to a minimum of 2 countries	None, as the regional review precedes national submissions; however, applicants are encouraged to market their products in all 15 countries
Submission windows	No windows; open throughout the year	No windows; open throughout the year	Four 30-day submission windows (Feb, May, July, Oct)
Submission of applications	Submission to the lead NMRA then submission to the remaining countries of interest immediately once the regional joint review is completed	Submission to all countries applicant is interested in marketing the product before the regional joint review commences	Submission to lead NMRA based on published expression of interest after a pre-submission meeting, then submission to the remaining countries of interest within 2 years of the regional joint review being completed
Assessment / review process	Primary and peer review by lead NMRA, peer and final review at joint assessment session	Primary review by rapporteur selected using applicable criteria, peer review by second country (co-rapporteur), final review at joint assessment session	Primary review by assessment team, peer and final review by expert working group at joint assessment session
Communication with sponsors	Responsibility of EAC Secretariat	Responsibility of each individual country to which the application was submitted	Responsibility of WAHO Secretariat

Final approval and marketing status	Approval issued by each individual NMRA in receipt of application and marketed only in those countries	Approval issued by each individual NMRA in receipt of application and marketed only in those countries	Approval issued by each individual NMRA in receipt of application and marketed only in those countries
Target timelines	315 days including applicant's time from the date validation is completed to the date of regional recommendation	270 days including applicant's time (from the date validation is completed to the date of regional recommendation	226 days including applicant's time (from the date validation is completed to the date of regional recommendation)
Target timeline for registration by NMRA after a regional recommendation	90 days	90 days	90 days
Fees	Paid to each individual NMRA; however, there are plans to pilot an additional regional fee	Paid to each individual NMRA; however, there are plans to pilot an additional regional fee	Regional fee paid to the WAHO Secretariat and the lead NMRA and a national fee paid to each NMRA where a national application is made

EAC = East African Community; ECOWAS = Economic Community of West African States; MRH = Medicines Regulatory Harmonisation; NMRA = national medicines regulatory agencies; SADC = Southern African Development Community; WAHO = West African Health Organization.

Type of procedure

The EAC MRH employs a decentralised procedure in which the applicant does not have the flexibility to choose the country to act as lead NMRA or reference member state for their application. The lead NMRA for all applications submitted to the EAC MRH is the Tanzania NMRA. In comparison, the ZaZiBoNa/SADC MRH employs a hybrid of the decentralised and centralised procedures in that the submission and final approval of applications are decentralised, while the review or assessment is centralised with the implementing NMRA; that is, Zimbabwe, serving as a coordinating agency that assigns applications to a rapporteur and co-rapporteur. Similarly, the ECOWAS MRH employs a hybrid of the centralised and decentralised procedures in that the process begins with a centralised joint regional review coordinated by the lead NMRA (currently Nigeria and rotated on a 2-year basis) and supported administratively by the WAHO Secretariat. The process is then decentralised, with each NMRA implementing a national procedure to issue national marketing authorisation upon receipt of applications for the jointly reviewed products.

Legally binding framework

The EAC MRH, ECOWAS MRH and ZaZiBoNa/SADC MRH all do not have legally binding frameworks; therefore, approvals are issued at country level and the products can only be marketed in those specific countries.

Eligibility criteria

The ECOWAS MRH does not have eligibility criteria because the regional review precedes national submissions; however, applicants are encouraged to market their products in all 15 countries, whereas for the EAC MRH and ZaZiBoNa/SADC MRH, the eligibility criteria is submission (or intention to submit for EAC MRH) to a minimum of two countries to be considered for joint regional review.

Submission windows

The EAC MRH and ZaZiBoNa/SADC MRH are open for submission of applications all year round, while the ECOWAS MRH accepts applications in four windows each year; that is, February, May, July, and October for 30 days.

Submission of applications

For the EAC MRH and ECOWAS MRH, applications are submitted to the lead NMRA first then to the remaining countries of interest once the assessment is completed. For the ZaZiBoNa/SADC MRH, applications are submitted only to countries where the applicant is interested in marketing the product.

Assessment/review process

The primary review and peer review of applications submitted to the EAC MRH is conducted by the lead NMRA before a final review by all seven EAC countries at a joint assessment session, while for the ZaZiBoNa/SADC MRH, the primary review and peer review is conducted by a rapporteur and co-rapporteur assigned for that particular application before a final review by all nine active member states at a joint assessment session. For the ECOWAS MRH, the primary review is conducted by an assessment team constituting the seven ECOWAS MRH countries before a peer and final review by the expert working group at a joint assessment session of the seven participating countries.

Communication with sponsors

The responsibility for communication with applicants lies with the EAC Secretariat for the EAC MRH and the WAHO Secretariat for the ECOWAS MRH. For the ZaZiBoNa/SADC

MRH, communication with applicants is carried out by each individual country to which the application was submitted.

Final approval and marketing status

The final approval is issued by each individual NMRA in receipt of the application and marketed only in those countries in all three regions.

Target timelines

The target timeline for the EAC MRH from the date validation is completed to the date of final regional recommendation is 315 days, inclusive of the applicant's time. Applicants are then expected to immediately submit applications to the countries in which they wish to market their products and be issued with a marketing authorisation within 90 days from the date of the regional recommendation. The ECOWAS MRH has a similar process and the target timeline from the date validation is completed to the date of final regional recommendation is 226 days inclusive of the applicant's time. Applicants are then given up to 2 years to submit applications to the countries in which they wish to market their products. The target time for the countries to issue a marketing authorisation once they receive an application is within 90 days. The target timeline for ZaZiBoNa/SADC MRH from the date an application is first discussed at an assessment session to the date a final regional recommendation is given is 270 days, inclusive of the applicant's time. Since the applications are submitted to each individual country in which the applicant wishes to market their products before the joint review, countries are expected to issue the marketing authorisation within 90 days of the regional recommendation.

Fees

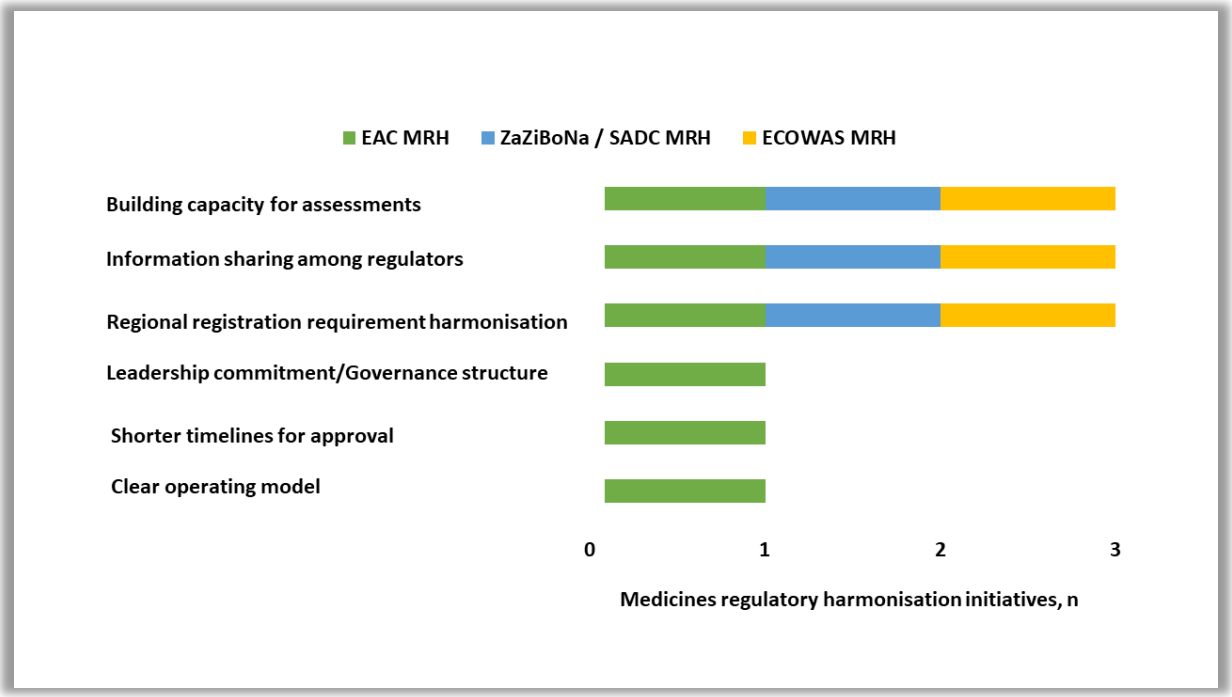
Fees are paid to the individual NMRA for registration in each country of interest in all three initiatives. In the ECOWAS MRH, this is preceded by payment of a regional fee to the WAHO Secretariat for the regional review. There are plans to pilot a regional fee in both the EAC MRH and ZaZiBoNa/SADC MRH in the near future. The regional application fees are intended to be used to finance joint reviews in addition to other sources of income, such as partners' support and self-funding by the participating countries in some of the regions.

Part II: Successes

For the comparisons in this section, a vote by the majority of countries (> 50%) in a region is recorded as a vote by the region.

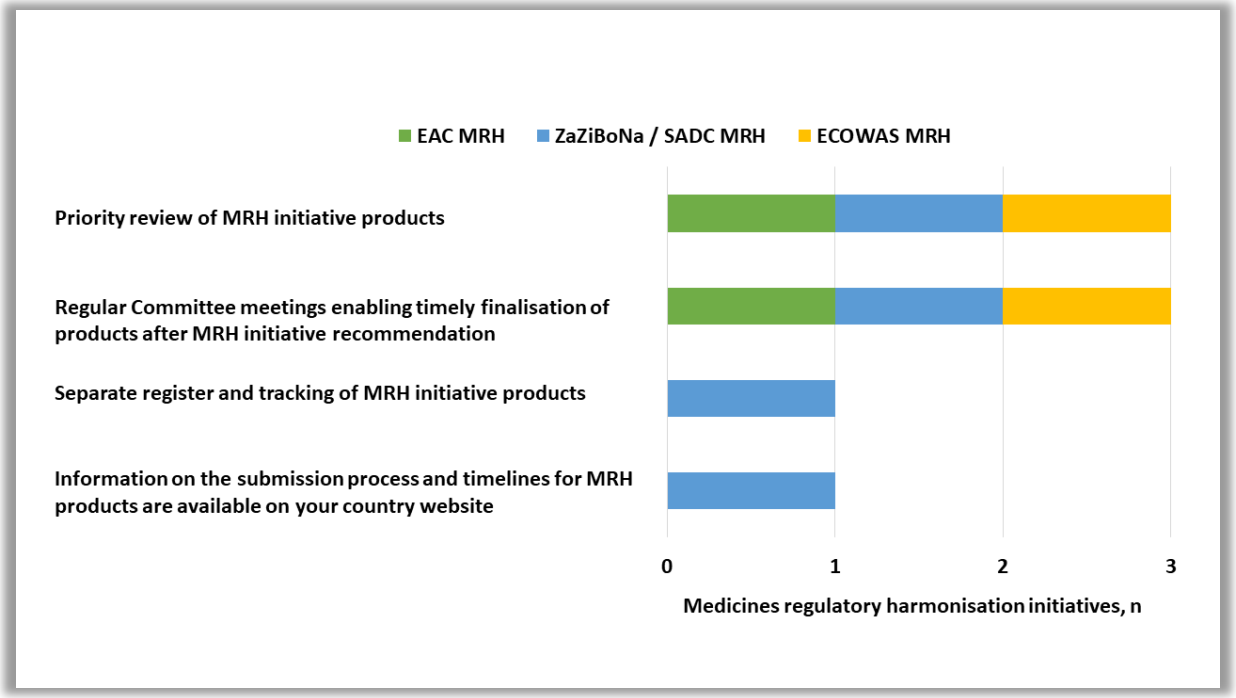
There is agreement in the three MRH initiatives about the following strengths of the MRH program; harmonisation of registration requirements across the region, information sharing among regulators and the building of capacity for assessments. However, leadership commitment / governance structure, clear operating model and shorter timelines for approval were identified as strengths only by the EAC MRH (Figure 7.2).

Figure 7.2 Strengths of the MRH initiatives.



In all three initiatives, the review of MRH initiative products is prioritised and Committee meetings held regularly enable the timely finalisation of products after an MRH recommendation. These are the strengths of the country processes in the majority of countries. However, none of the MRH initiatives have a list of the products approved using joint reviews available on the individual country websites and only ZaZiBoNa/SADC MRH have information on the submission process and timelines for MRH products available on the majority of individual country websites as well as a separate register and tracking of MRH products (Figure 7.2).

Figure 7.3 Strength of country processes in implementing the MRH programme.



MRH benefits to member countries (regulators)

There is consensus from all three MRH initiatives on the benefits received by member countries (regulators) from participating in the MRH programme and these are the training, which has improved the performance of the assessors, enabling the application of high standards of assessment regardless of the size of the country or maturity of the regulatory authority. This platform has also made it easier for information and knowledge exchange among the countries. However, only EAC MRH were of the view that the shared workload resulted in shorter timelines for approval compared with the individual timelines of the majority of EAC countries.

MRH benefits to manufacturers (applicants)

There is agreement in all three regions about the benefits of the MRH programme for manufacturers/applicants and these are the reduction of the burden of preparing multiple dossiers, as under the MRH programme, only one dossier (modules 2 -5) is compiled for submission to multiple countries. Other benefits are the saving in time and resources, as applicants receive the same list of questions from multiple countries enabling compilation of a single response package as well as simultaneous access to various market. However, only the

EAC MRH were of the view that applicants benefited from shorter timelines for approval under the MRH programme compared with the individual timelines of the majority of EAC countries.

MRH benefits to patients

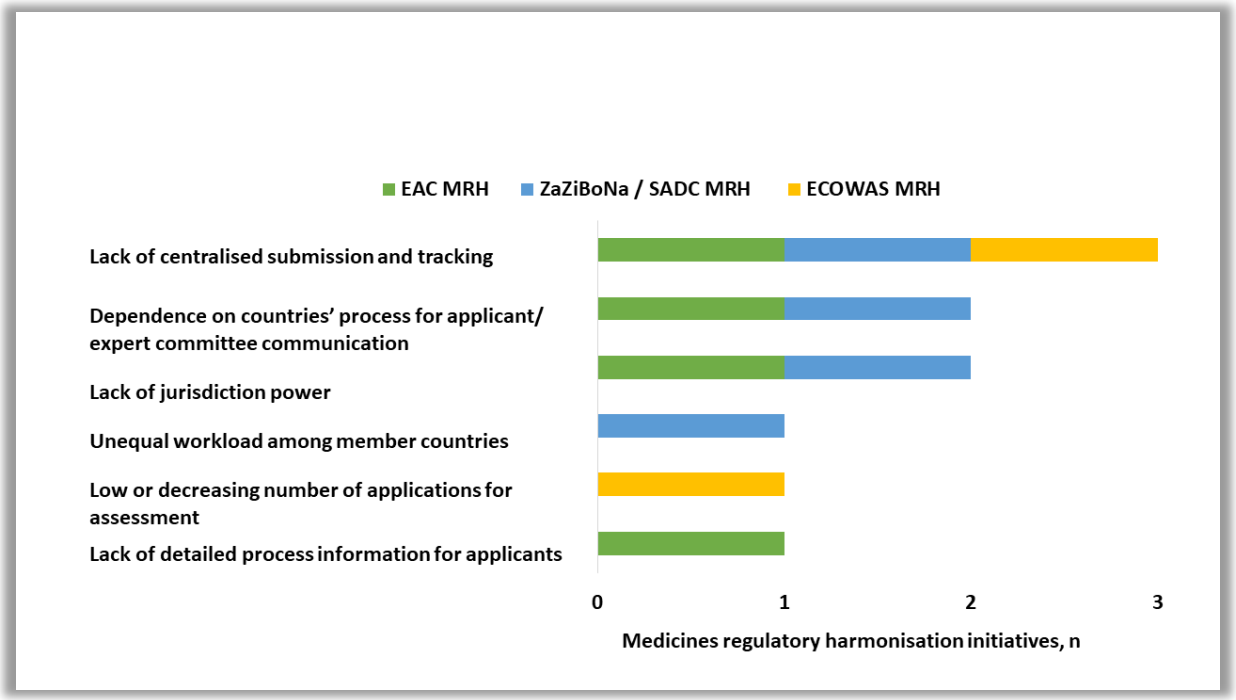
The consensus amongst the three regions was that the MRH programme has resulted in quicker access and increased availability of quality-assured medicines for patients; however, this was not at a reduced price.

Part III: Challenges

For the comparisons in this section, a vote by the majority of countries (> 50%) in a region is recorded as a vote by the region.

There was consensus amongst all three regions that the lack of centralised submission and tracking was a weakness of the MRH initiatives. The dependence on the countries' processes for communication with applicants and expert committees and the lack of jurisdiction power (the ability to mandate registration) were also identified as weaknesses by the EAC MRH and ZaZiBoNa /SADC MRH (Figure 4).

Figure 7.4 Weaknesses of the MRH initiatives.

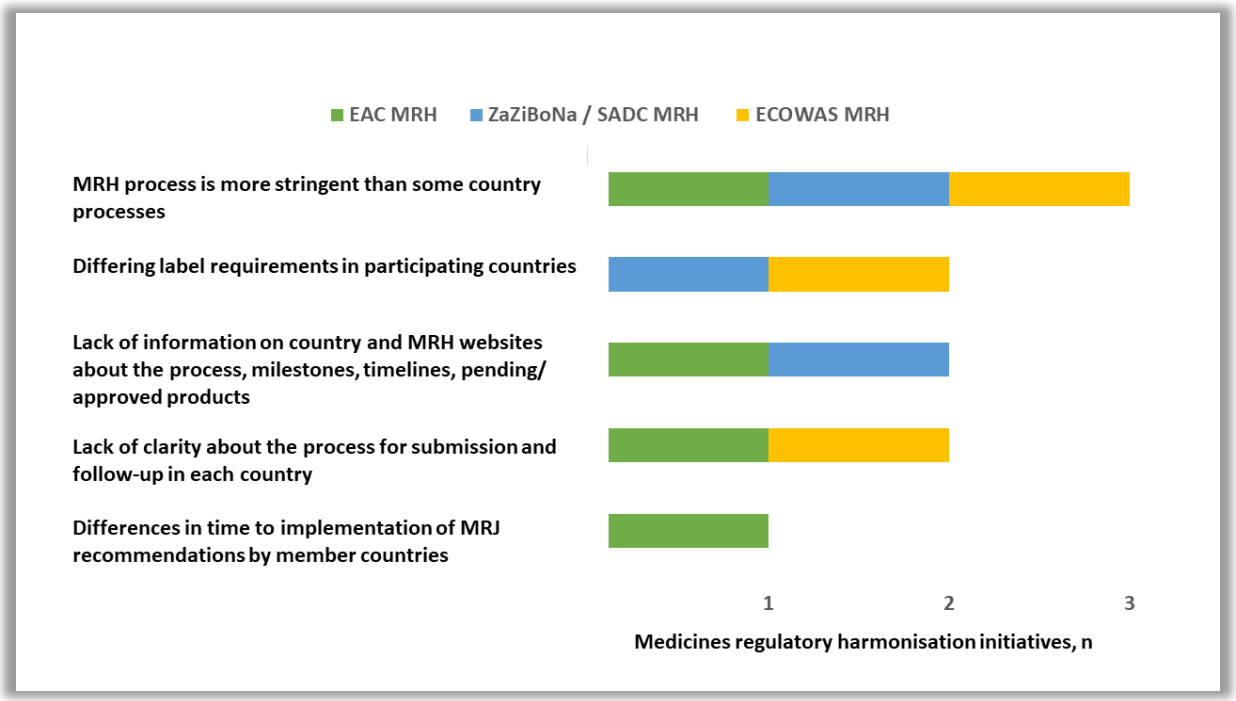


Challenges faced at country level in implementing the MRH programme

The three initiatives unanimously agreed that a challenge in implementing the MRH programme is inadequate human resources. Failure by manufacturers to follow the requirement to submit the exact same dossier to all countries of interest and to adhere to deadlines for responses to questions were additional challenges faced by the EAC MRH and the ZaZiBoNa/SADC MRH.

All three initiatives were of the view that a challenge faced by applicants is that the MRH process is more stringent than some country processes. Additional challenges faced by applicants identified by two of the three MRH initiatives were differing labelling requirements in participating countries, lack of information on country websites and the MRH website about the process, milestones, timelines and pending and approved products and a lack of clarity about the process for submission and follow-up in each country (Figure 7.4).

Figure 7.5 Challenges faced by applicants submitting applications to the MRH initiatives.



Accessibility and affordability of medicines

An interesting finding from this study was the consensus amongst the three regions that although the MRH programmes had resulted in quicker access and increased availability of quality-assured medicines for patients, this was not necessarily at a reduced price. This could be because most of the regulatory authorities participating in these initiatives are not responsible for regulating the pricing of medicines; moreover, there are no health technology assessment agencies in these countries to perform this function as is the practice in other jurisdictions.[22] As a result, the harmonisation of requirements and work sharing has not resulted in the availability of medicines at a lower price for patients; however, one way the regions plan to negotiate lower prices for medicines is through the implementation of pooled procurement.

DISCUSSIONS

The AMRH has made significant gains in the strengthening of national regulatory systems and the harmonisation of regulatory requirements since its formation in 2009. According to the regulatory authorities that participated in this study, the three registration harmonisation projects have all managed to meet the core objectives, which were to harmonise guidelines and registration requirements and to build the capacity of member states. The objectives of shorter timelines and simultaneous access to various markets have not been as straightforward to achieve for all the regions, as they are dependent on the time taken by the individual countries to issue a registration/marketing authorisation upon completion of the joint scientific review and in addition for EAC MRH and ECOWAS MRH the time taken by the applicant to submit an application for registration of a jointly viewed product to the individual countries. The EMA, which has been in existence for over 25 years, provides a blueprint from which the regional harmonisation initiatives in Africa can learn.

Registration or marketing authorisation of a medical product is a legal decision that can only be issued by a legally mandated entity, usually a national regulatory authority within a jurisdiction (Rago, 2008). As such, networks, organisations or entities without that legal mandate cannot issue a registration. Aware that this limitation existed in the regional economic communities (RECs), EAC, ECOWAS and SADC, the regulators decided to establish their work-sharing initiatives as a decentralised model or a hybrid of the decentralised and centralised models, leaving the responsibility for issuing registrations to the national regulatory authorities in their respective countries. This decision has borne fruit, as we report the results

of this study show that the initiatives have successfully developed regional guidelines and templates and conducted joint reviews of many products (Ngum et al,2022, Owusu-Asante et al,2022 & Sithole et al,2022a). The initiatives also resulted in building the capacity of member states; for example, in the EAC, Burundi, Rwanda and Zanzibar were supported in the establishment of semi-autonomous national regulatory authorities that previously did not exist (EAC,2024). In SADC, Angola and Mozambique were also supported in the establishment of semi-autonomous national regulatory authorities. However, there has been some disappointment with the joint review initiatives for the pharmaceutical industry, as their expectation was to have a fully centralised process with a single approval enabling simultaneous access to various markets (Dansie et al, 2019).

In hindsight, the simultaneous access should not have been promised or expected, as it can only be achieved in a fully centralised process with jurisdiction power, a situation currently not possible due to the founding and operating principles of the RECs. A better approach would have been to communicate the target timelines for the joint review process to applicants from the outset, while highlighting that the timelines for approval in countries would differ and be dependent on the national process as is carried out for the decentralised procedure of the EMA and other similar work-sharing initiatives such as the Australia-Canada-Singapore-Switzerland-United Kingdom (ACCESS) Consortium (Australian Government Department of Health, Accessed 2024). One initiative that can immediately be implemented to bring alignment in the operating models of the three initiatives and improve efficiency is for the EAC MRH and ZaZiBoNa/SADC MRH to develop a framework to enable a centralised regional submission and review prior to submission to the individual countries of interest for registration, as is carried out in the ECOWAS MRH. In addition, the two-year period given by the ECOWAS MRH for applicants to submit applications to the country after a regional review needs to be revised to align with the other two regions, EAC MRH and ZaZiBoNa/SADC MRH, in which registration in the individual countries is pursued immediately after the regional review. In addition, the lengthiness of this two-year period negates the benefit of shorter registration times that the MRH programme seeks to achieve.

However, it is recommended that all three initiatives consider using three routes/procedures for the approval of medical products in their regions; that is, a fully centralised procedure, a decentralised procedure and a national procedure. For the three regions, this would entail

pursuing the development of a regional legally binding framework, if possible, to allow the establishment of a fully centralised procedure as is carried out in the European Union. The use of the centralised procedure could be made mandatory for certain critical medical products to ensure equitable access in all member states, regardless of regulatory capacity or maturity. The use of regional experts in the assessment of complex products and central safety monitoring is another benefit of a centralised procedure.

Investment in robust information management systems is critical to immediately address the additional weaknesses or challenges identified with the current operating models of the initiatives in this study such as the lack of detailed information for applicants on procedures and the lack of adequate tracking and monitoring of timelines for products in the participating countries once the joint review is completed. This investment will empower the region to publish this information for stakeholders, improving transparency and confidence in the process. This is supported by other studies conducted in these regions, which advocated greater transparency and the use of metrics to identify opportunities to improve efficiency (Giaquinto et al, 2020 & Sithole et al 2022).

From the results of this study, it is evident that the countries participating in the three RECs have successfully implemented reliance by leveraging the regulatory work of other NMRAs as well as regional reliance mechanisms. For example, several countries in the RECs have signed bilateral agreements to facilitate the sharing of information for abridged and verification reviews. There is potential for the countries to further implement reliance through unilateral and mutual recognition. Currently, in the East African region, Zanzibar unilaterally recognises the decisions of Tanzania; in the Southern African region, Eswatini, Mauritius and Namibia unilaterally recognise the decisions of South Africa. The regions should continue to support and advocate the strengthening of the capacity of their member states using the WHO GBT assessments (formal and informal). As capacity and trust is built, more countries will consider implementing unilateral and mutual recognition within a region as well as between the different RECs on the continent. In addition, measures should be implemented to increase efficiency in the regulatory review process such as the use of the Optimising Efficiencies in Regulatory Agencies (OpERA) tool to track, monitor and evaluate performance (Sithole et al, 2021). Greater transparency through the publishing of public assessment reports as well as documenting the benefit-risk assessments conducted and the basis for reaching decisions using

tools such as the Quality of Decision-Making Orientation Scheme (QoDoS) will facilitate a greater extent of reliance (Bujar et al,2019).

RECOMMENDATIONS

The following recommendations in order of implementation priority are based on the synthesis of the results, which were then endorsed by the regulatory authorities.

1. **Aligning the operating models to improve efficiency:** The EAC MRH and ZaZiBoNa/SADC MRH should consider developing a framework to enable a centralised regional submission and review prior to submission to the individual countries of interest for registration as is the situation in the ECOWAS MRH. In addition, the two-year period given by the ECOWAS MRH for applicants to submit applications to the country after a regional review needs to be revised to align with the other two regions, EAC MRH and ZaZiBoNa /SADC MRH, in which registration in the individual countries is pursued immediately after the regional review.
2. **Reliance:** The RECs should continue to support and advocate the strengthening of the capacity of their member states using the WHO Global Benchmarking Tool assessments and other tools such as Optimising Efficiencies in Regulatory Agencies (OpERA) and Quality of Decision-Making Orientation Scheme (QoDoS) to facilitate inter-country and inter-REC reliance including unilateral and mutual recognition.
3. **Communication with applicants:** The initiatives implementing any form of a decentralised procedure at submission; that is, EAC MRH and ZaZiBoNa/SADC MRH should communicate with existing and prospective applicants, the target timelines for the joint review process as well as to highlight that the timelines for approval in countries will differ and be dependent on the national process, as it is for other decentralised procedure such as that of the EMA or ACCESS.
4. **Publishing an Expression of Interest:** The EAC MRH and ZaZiBoNa/SADC MRH should implement the practice of publishing an expression of interest as is the situation by the ECOWAS MRH.
5. **Information Management Systems (IMS):** In the absence of legally binding frameworks, the RECs should invest in robust information management systems to address the weaknesses and challenges identified in this study such as the poor tracking of products and monitoring of timelines in the countries after a joint review is completed.

6. **Legal framework:** All three initiatives should consider using three routes/procedures for the approval of medical products in their regions; that is, a fully centralised procedure, a decentralised procedure and a national procedure. For all three regions, this would entail pursuing the development of a regional legally binding framework, if possible, to allow the establishment of a centralised procedure.

CONCLUSIONS

This study has highlighted the successes of the medicine registration harmonisation initiatives in Africa as well some opportunities for improvement and alignment. The results of this comparison allow for the three regional harmonisation initiatives to learn from each other, and the implementation of the recommendations made in this study will bring greater alignment and efficiency in their operating models thereby strengthening the foundation of the soon to be operationalised AMA.

SUMMARY

- Information is needed regarding the operating models and successes and challenges experienced to date for the three initiatives for medicines regulation established in the economic communities of Africa under the auspices of the African Medicines Regulatory Harmonisation Initiative.
- Qualitative questionnaire and literature search data reveal that the marketing authorisation application review processes of the three MRH programmes, The East African Community; Southern African Development Community/ ZaZiBoNa; and Economic Community of West African States are largely similar, with a few differences noted in the eligibility and submission requirements, type of procedures employed (e.g., centralised or decentralised), the timelines and fees payable.
- Participants uniformly agreed that harmonisation of regulatory requirements, information sharing and capacity building are the primary benefits of the MRH initiatives, whilst the principal challenges of the programmes are a lack of centralised submission and tracking and inconsistency in stringency of submission requirements.
- Recommendations to mitigate these challenges include the alignment of operating models; development of a regional legally binding framework to allow establishment of a centralised procedure; formation of information management systems and support of capacity strengthening to facilitate mutual recognition and reliance.
- The recommendations made in this study will bring greater alignment and efficiency to the operating models of the three regional harmonisation initiatives, strengthening the foundation of the soon to be operationalised African Medicines Agency.

CHAPTER 8

A PROPOSED IMPROVED REVIEW MODEL FOR THE EAC-MRH

INTRODUCTION

In 2012 the EAC-MRH Initiative was established to improve access to safe, effective and efficacious medical products to patients in the East African region. The EAC Partner States have a population of 290 million inhabitants, and these are the Republic of Burundi, Democratic, Republic of Congo, Republic of Rwanda, United Republic Tanzania, Republic of Kenya, Republic of South Sudan, and the Republic of Uganda. The timely access to medical products was to be achieved through harmonization of regulatory requirements, joint assessments, joint inspections of manufacturing sites and the strengthening of regulatory systems. As part of the implementation of one of the provisions of the EAC Treaty on regional harmonisation in health, the EAC Secretariat, in collaboration with the EAC NRAs, established the EAC-MRH project as the regional coordinating body of the AMRH initiative in 2012 (Ngum et al, 2023).The initial focus of the project was on the registration of generic medical products and then to later expand to other medical products and regulatory functions (Mashingia et al,2020) of which the goals and objectives have been achieved to some extent. The overall goal of the EAC-MRH project is to enhance patents' access to safe, efficacious, and quality medicines.

Evaluation of the Regulatory Review Process of the EAC-MRH Initiative

When the EAC-MRH initiative was established, key milestones were expected to be achieved after a few years of the implementation of this initiative. During the first five years (2012-2017) of this program, the following were expected to be implemented; an agreed common technical document for registration of medicines in the EAC Partner States; a common information management system for medicines registration in each of the EAC Partner States' NMRAs which are linked in all Partner States and the EAC Secretariat; a quality management system in each of the EAC Partner States' NMRAs; build regional and national capacity to implement medicines registration harmonization in the EAC; develop and implement a framework for mutual recognition; and create a platform for information sharing on the harmonized medicines registration system for key stakeholders at both national and regional level (Silo et al, 2020). At the end of the five year period, the objectives were revised and the following recommended for implementation during the period 2020 to 2022; an improvement of existing processes and expanding into new regulatory areas and activities; develop a well-

coordinated and well-functioning regional assessment and inspection process, on which national registration decisions can rely and create a sustainable, semiautonomous agency that will provide regulatory guidance and coordination for the entire region by 2022 (Arik et al, 2020).

To assess the regulatory review process of the EAC-MRH Initiative over the last ten years, a literature review was conducted to understand the factors that can contribute to or have hindered the successful implementation of this initiative. This study documented the history of the initiative, the legal framework, the organizational structure, the operating procedure as well as the challenges and successes of the initiative. Some key recommendations were further proposed from this study (Ngum et al, 2023).

The impact of this work sharing initiative depends on the uptake of the regional decisions by the national agencies. One of the key recommendations from the review of the work sharing initiative was therefore to evaluate the regulatory review processes of the national regulatory authorities of the countries in the EAC region. It was noted that one of the challenges with work sharing is the inconsistent regulatory processes and variable technical standards and guidelines between countries that do not meet international standards (Ngum et al., 2022b).

The regulatory review processes of the seven NRAs in the EAC region were therefore evaluated and compared for the first time by this research. These NRAs include ABREMA, PPB Kenya, Rwanda FDA, DFCA, TMDA, NDA Uganda, and ZFDA The results of this study led to a comparison of the NRAs in these countries in terms of organisation of the regulatory authorities, key milestones in the review processes regarding when the application is received to when it is granted marketing authorization. Also, the target timelines and number of applications received and approved from 2020 to 2023 based on the type of application (NAS and generics) and kind of review model used (full review, verification or abridged) and the qualities for implementation of good review practices were also analysed. The measures put in place for quality decision making by these agencies during scientific reviews were also examined. From the results of this study, it was noted that the regulatory review processes of these agencies vary and will need further alignment. A point in case is the clock stop time, which varies from agency to agency, making it difficult to compare the actual review timelines against the target timelines; difference in target timelines for and review models used as well

as differences in target timeline for start and finish of expert committees. A key recommendation from this study is to invest in regulatory systems strengthening, streamline country processes and minimize the differences that exist within the NRAs as these interventions will improve patients' access to safe, quality and effective medical products especially during the operationalisation of the African Medicines Agency.

This study also proposes a very important recommendation which is the need to review the operating model of the EAC-MRH programme so as to identify areas of improvement of the effectiveness and efficiency of the initiative. Some articles have been published on the strengths and weaknesses of the EAC-MRH initiative (Sillo et al., 2020; Mashingia et al., 2020) after eight years of implementation. Another study by Arik et al, (2022), proposed a two years (2020-2022) roadmap for the EAC's MRH initiative. There has not been a comprehensive study conducted to examine the performance of the ten years (2012-2022) existence of this initiative, therefore this is the first time that a study has been conducted to evaluate the effectiveness and efficiency of the current operating model of the EAC-MRH initiative, including the challenges faced and to identify opportunities for improvement (Ngum et al, 2022a and Ngum et al, 2022b). All seven NRAs in the region and 14 out of the 25 pharmaceutical companies who have submitted their applications through the EAC-MRH process from 2015 to 2022, participated in this study. This study resulted in the identification of the successes and challenges of the EAC-MRH after ten years of implementation and then propose measures that can improve the effectiveness and efficiency of the initiative. The challenges and benefits of this initiative to the regulators, the pharmaceutical industry and patients was also a major outcome of this study. Key recommendations for improvement of the work sharing initiative were also generated.

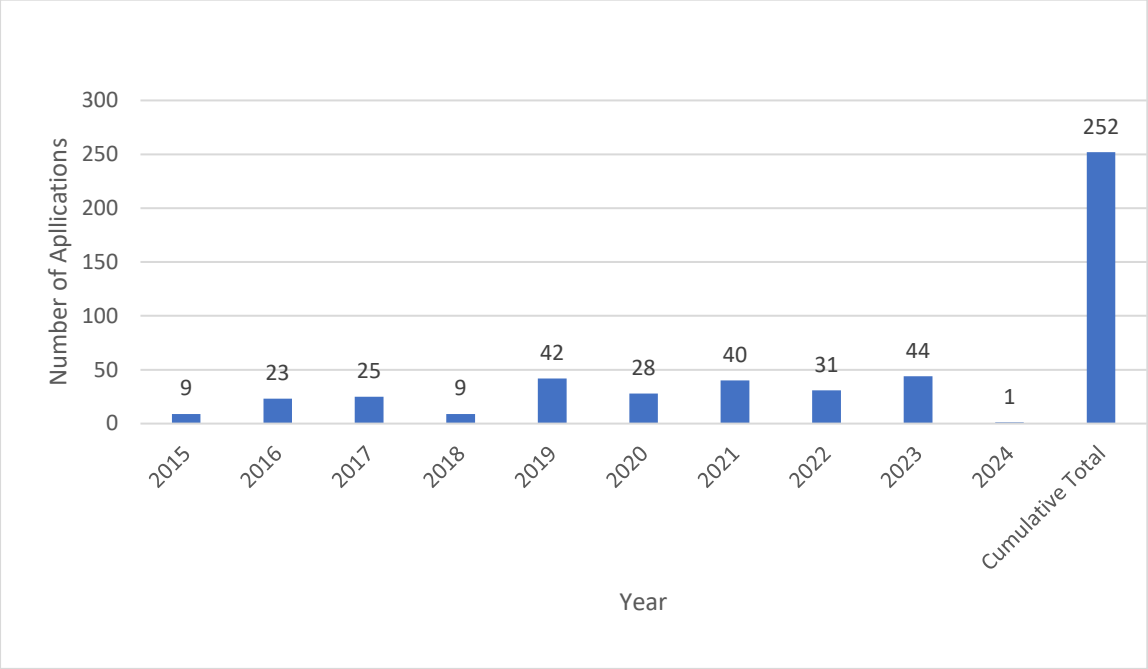
Successes of the EAC-MRH

This initiative has developed harmonised technical requirements and guidelines for the regulation of medical products together with a compendium of established Common Technical Documents (CTD) to provide harmonised medicines registration procedures (Ngum et al, 2023). Median timelines for joint reviews from submission of application to when a decision is made has decreased (Mashingia et al., 2020) and the timelines for registration of medical

products have also reduced by almost half (Ndomondo-Sigonda et al,2020). For the NRAs in the region it was affirmed that this initiative has improved their regulatory capacity especially as it has provided a platform for information sharing and learning from best practices which has resulted in building the capacity of the regulators (Ngum et al, 2022a). For the pharmaceutical companies using the work sharing initiative to apply for marketing authorisation, a key benefit is the reduced burden as the applicants prepare only one application (modules 2-5) for submission to many countries and eventual access to many markets simultaneously (Ngum et al, 2022b). This also saves time and resources for applicants as they prepare only one response package for a consolidated list of queries from many countries. Furthermore, there have been shorter timelines for approval of applications through the EAC process as compared to some country processes and this was also identified as a key success factor for the initiative. The benefits of this process for patients is that the harmonised and working efforts has enhanced quicker access to quality-assured medicines and increased the availability for patients (Ngum et al, 2022b). Several successes of this initiative have been identified and lessons learnt. Positively the number of applications received for joint reviews increased from 9 applications in 2015 to 44 applications received in 2023 (Figure 8.1). Review

timelines have significantly reduced from 2015 to 2023 with a 53% decline in median time at the NRA level (Figure 8.2).

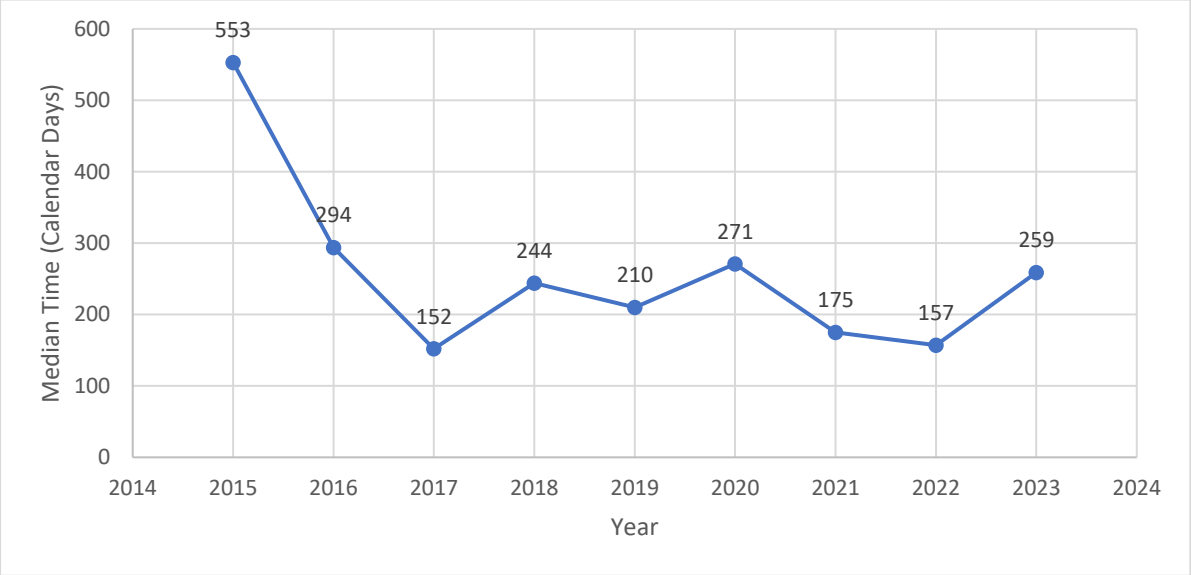
Figure 8.1 Cummulative Trend of Product Applications (2015 To 2024)



Source: EAC-MRH Report, 2024

Regional harmonised regulatory frameworks, guidelines, procedures, tools and templates have been developed. Thirty joint scientific assessment sessions (both face to face & virtual) have been conducted and all the 252 applications received have all been reviewed (100%), 147 (58%) medicinal products have been recommended for Marketing Authorization (MA) and 105 (42%) not recommended for registration. An MRH governance structure and 10 expert working groups have been established. There now exists national focal points in each NRA with TMDA as the lead NRA coordinating joint assessment and Uganda NDA as the lead coordinating joint inspections. Risk-based assessment approaches are also being implemented and harmonised guidelines for abridged procedures, a metric tool to measure registration timelines at regional & national level has also been developed. However, numerous challenges that have hampered the successes of the EAC-MRH initiative, have also been identified at both national and the regional level.

Figure 8.2 Median time per year (2015 -2023)



Source: EAC-MRH Report, 2024

Challenges of the EAC-MRH Initiative

Several studies (BCG, 2017; Mashingia et al., 2020; Ncube et al., 2021; Ngum et al, 2022a) have highlighted the lack of a legal framework of the EAC-MRH as a fundamental challenge for this initiative. Limited resources and capacity with a fragmented legal framework at both national and regional level is a major challenge. A lack of financial sustainability for this initiative has negatively affected the successful implementation of its activities (Ndomondo-Sigonda et al, 2020). The harmonisation initiative is being hampered by countries having inconsistent regulatory processes and using different technical standards and guidelines as well as the fact that there is no binding legislation (Ncube et al., 2021). The payment of fees by the manufacturer at the regional and national level is another major challenge as this has caused a delay in the registration of the regionally recommended products in the countries (Ngum et al,2023). Another challenge faced by this initiative is the lack of a tracking system to monitor and capture clear registration timelines at both the country and regional level (Ngum et al, 2022a). This lack of a centralised submission and tracking of applications has also been a critical challenge as it has negatively affected transparency and communication with applicants and even amongst assessors. The lack of clarity about the process for submission, different labelling requirements in participating countries, the lack of a centralised system for payment of the application fees to all EAC NRAs, unequal workload among member countries are some other challenges that have been identified. (Ngum et al, 2022a; Ngum et al, 2022b). These challenges have negatively affected the progress in implementing the EAC-MRH Initiative. The aim of this study is to propose a new and improved model for the EAC-MRH.

METHODS

During this research project, five studies were conducted for the period 2020 to 2023 and opportunities for improvement were identified in each study. The hope is that this proposed improved model, if implemented, will assist in addressing some of the gaps and eventually lead to a successful implementation of the EAC-MRH work sharing programme with minimal challenges.

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records, online platforms, websites, published books, thesis, and unpublished documents (Chapter 1)

Study 1: A validated questionnaire (McAuslane et al, 2009) was used to obtain information from the seven NRAs participating in the EAC-MRH. This questionnaire (OpERA) was completed by senior officials in the seven agencies who are leading the medicine registration departments. The heads of agencies of these NRAs further validated the completed questionnaire which documented the general organisation of the agencies in terms of their structure, organization and resources. Furthermore, the activities that contribute to the measures that would improve transparency and consistency were also reviewed in order to understand how quality is built into the regulatory review process to enhance good review practices that were implemented by these agencies (Chapter 3).

Study 2: Using the standardized OpERA questionnaire, the same senior officials completed the questionnaire and again it was validated by the heads of these agencies. The questionnaire captured the main steps in the review and approval process and identified the dates for key milestones in the review process . (Chapter 4).

Study 3: The Process Effectiveness and Efficiency Rating (PEER) questionnaire was completed by senior officials in the seven agencies and the completed questionnaire was validated by the heads of agencies. This questionnaire was used to obtain the views of the individual medicine's regulatory authorities of the EAC-MRH initiative about the performance of the joint assessment initiative to date. It also identified the challenges experienced by the individual authorities throughout the life cycle of the EAC-MRH initiative and then determined the strengths and weaknesses of the initiative in order to eventually identify ways of improving the performance of the joint assessment and envisage a strategy for moving forward to improve effectiveness and efficiency (Chapter 5).

Study 4: The Process Effectiveness and Efficiency Rating (PEER) questionnaire, modified for the pharmaceutical industry, was completed by the heads of regulatory units in the pharmaceutical companies that have used the EAC-MRH process for the review and approval of their applications. This questionnaire was used to obtain the views of the pharmaceutical companies about the performance of the joint assessment initiative to date as well as identify the challenges experienced by the pharmaceutical companies throughout the life cycle of the

EAC-MRH initiative. Subsequently, this determined the strengths and weaknesses of the initiative and eventually identified ways of improving the performance of the joint assessment initiative as well as envisaged a strategy for moving forward to improve effectiveness and efficiency (Chapter 6).

Study 5: : The Process Effectiveness and Efficiency Rating (PEER) questionnaire was completed by the senior officials responsible for monitoring and documenting regulatory performance metrics in the seven agencies in the EAC MRH (Burundi, Kenya, Rwanda, South Sudan, Tanzania, Uganda and Zanzibar) as well as all nine active members of the ZaZiBoNa/SADC MRH (Botswana, Democratic Republic of Congo, Malawi, Mozambique, Namibia, South Africa, Tanzania, Zambia and Zimbabwe) and all seven members of the ECOWAS MRH (Burkina Faso, Cote d'Ivoire, Ghana, Nigeria, Senegal, Sierra Leone and Togo) participated in the three initiatives that were used for this comparative study. The completed questionnaires were further validated by all the Heads of Agency in the three regions. The questionnaire provided the elements to compare the operating model, review process and requirements of the three harmonisation initiatives and to compare the successes and challenges of these initiatives as well as identify opportunities for improvement and alignment of the initiatives and develop recommendations for the way forward (Chapter 7).

RESULTS.

To ensure clarity, the results will be presented in three parts; Part 1: A proposed improved model for the EAC NRAs; Part II: Proposed improvements to the current operating model of the EAC-MRH Initiative and Part III: A proposed new improved model for the EAC-MRH initiative.

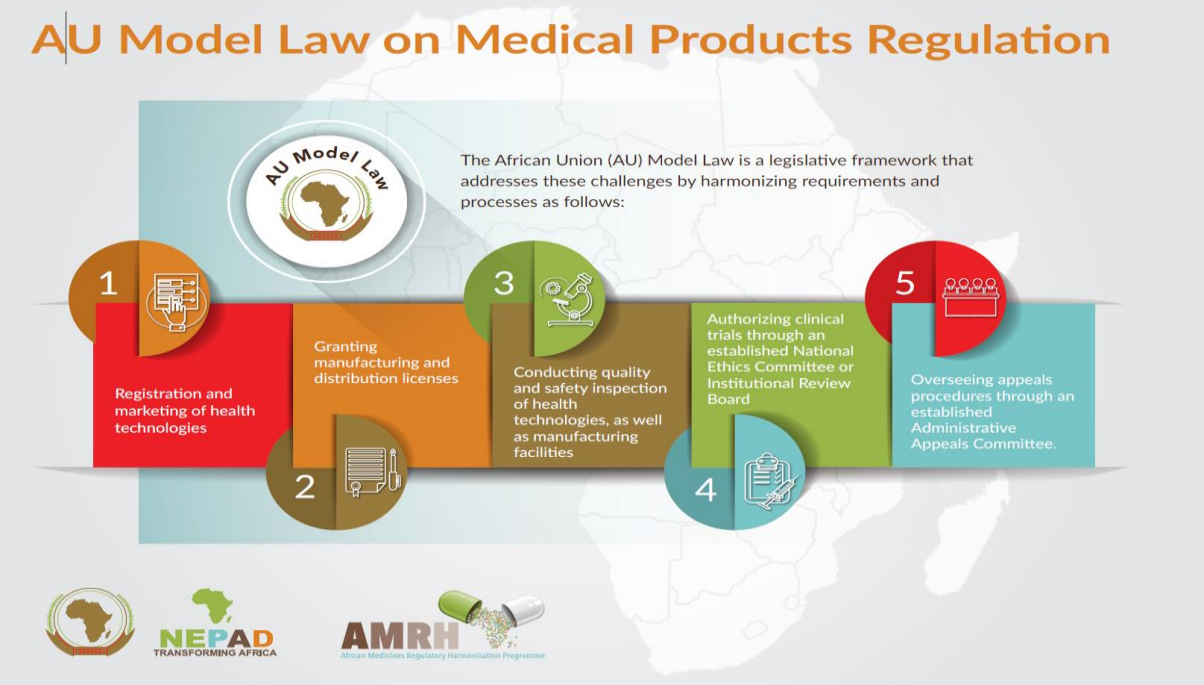
Part 1: Proposed improved model to the EAC NRAs

The regulatory review systems of the NRAs in the EAC region need to be strengthened so as to improve the effectiveness and efficiency of the EAC-MRH work sharing initiative and eventually the AMA when it is operational. These are some proposals for implementation by the NRAs to improve their regulatory review systems.

Legal Frameworks

One of key challenges faced by NRAs that stimulated the establishment of regulatory harmonization was the fragmented legal frameworks of countries in Africa. The NRAs in the EAC region are called upon to domesticate the African Union Model Law on Medical Products Regulation (AU Model Law). The AU Model was endorsed by the AU Heads of State and Governments in 2016. “The purpose of this Law is to establish an effective and efficient system of medical products regulation and control and ensure that such products meet required standards of safety, efficacy and quality” (AUDA NEPAD, 2017). This is a non-prescriptive legislation expected to be domesticated and implemented by all the AU member states and RECs with the goal to increase collaboration amongst countries, harmonise regulatory systems, and eventually provide a conducive environment for medical product technology and scale up (Figure 8.3). It describes the essential features and requirements that must be included in the regulatory system and offers African nations a template for harmonising their regulatory systems (Ncube et al, 2023). The AU Model Law is also intended to assist countries in incorporating the ability to charge for, collect, and utilize fees for services carried out during the examination or enactment of their laws. Domestication of the law will ensure that the agencies in the region have comprehensive laws for regulation of medical products and eventually facilitate the harmonization process of the EAC-MRH Initiative. According to Ncube et al (2023), only four NRAs (ABREMA, Burundi, PPB Kenya, TMDA Tanzania Mainland and ZFDA Tanzania Zanzibar) out of the seven in the region have domesticated the AU Model Law.

Figure 8.3 The AU Model Law on Medical Products Regulation



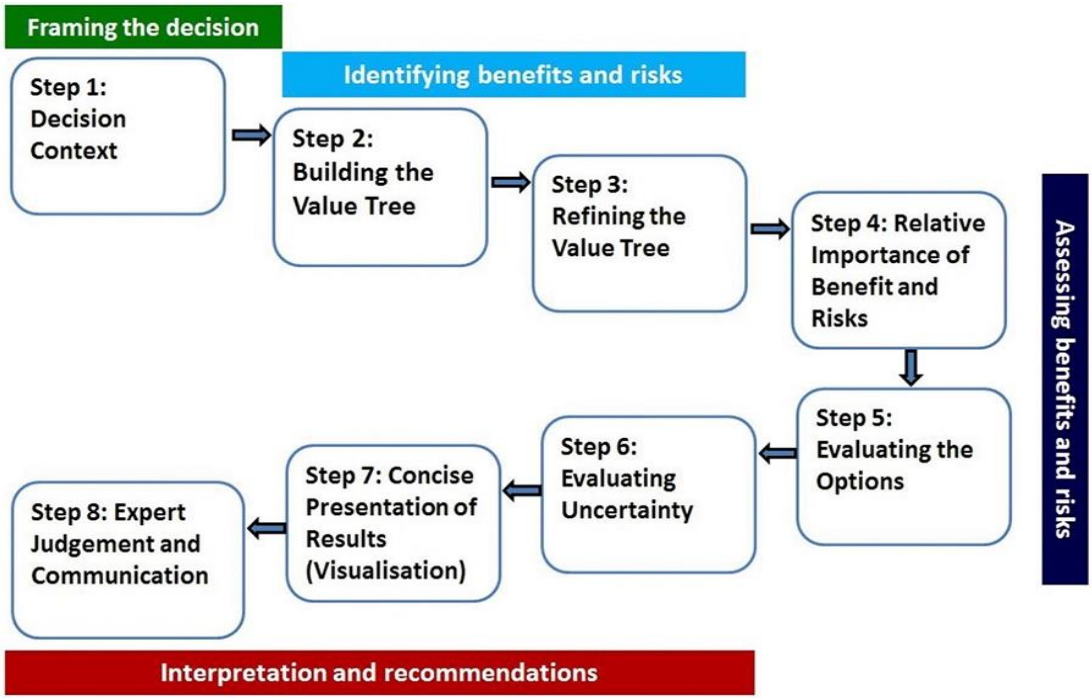
Source: AUDA-NEPAD Website, 2021

Benefit-Risk Assessment

For NMRAs to rely on each other or harmonise medicine regulation, there is a need for them to use standardised templates that will enable quality decision-making processes and transparency. Although regulatory agencies may receive applications that have the same information from manufacturing agencies, they make different decisions as most of them use checklist for their review. There is now a growing interest from regulatory agencies to use a more structured approach for decision making and transparency. A consistent and transparent benefit-risk assessment decision is based on a structured flow of information and the systematic approach of the benefits and risks which is well documented and communicated to relevant stakeholders for accountability purposes (Walker et al, 2015 & Leong et al 2015). It is important that the key players such as patients, medical practitioners and regulators identify with the regulatory decisions being made. Nowadays, to improve transparency and accountability, and to be in line with good review practices, regulatory authorities are facing a great deal of pressure to implement a systematic and structured approach in making regulatory decisions on benefit risk assessments of medical products (Sithole et al, 2022a). Regulators are

expected to make a balanced judgement between the benefits and risks of a new medical product that is being brought to the market and communicate this to the public as one of the measures to enhance regulatory effectiveness (Leong et al, 2015).

Figure 8.4 UMBRA Benefit-Risk Framework (Source:McAuslane, 2017)



How do agencies in the EAC region document and communicate benefits and harm of a medical product? The benefit-risk assessment process is not yet implemented in this region. The CIRS has developed an eight step (Figure 8.4) Universal Methodology for Benefit-Risk Assessment (UMBRA) which can be used by NMRAs in the EAC region to document benefit-risk assessments in a structured and systematic way (McAuslane et al 2017).

Build Capacity of NRAs

From this study, only one NRA reviews applications on New Active Substances. It will be important to empower the NRAs to be able to review NAS as this becomes incresingly relevant during emergency situations. The NRAs should also invest more in human resources to be able to respond in a timely manner to the high demand of their services.

To have the registration requirements for an efficient and effective regulatory system the countries should have the following requirements before the clock can start including receipt

of application by the country from the applicant after a regional recommendation has been made.

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Develop Digitilisation Strategy (Regulatory Information Management System/RISP/ Tracking/ Metric tools/)

The AMRH programme has recommended a Model Regulatory Information Management system (AU Model RIMS) for countries that do not have information management systems for use by the NRA. A robust (RIMS) should be developed by each NRA in the region to provide online and real-time medicine regulation information and support workflow management in the agency as this will assist in the management of data during the review process. The RIMS should be able to contain metric tools that countries can use to track applications and capture data on key milestones throughout the registration process. NRAs should also implement the e-CTD which is the digitalized way to accelerate assessment reviews. The RIMS should be interoperable and can be integrated with the RIMS of other NRAs in the region and also linked to the Regional EAC-MRH system and eventually the continental RIMS when AMA becomes operational (Figure 8.5). The Regulatory Information Sharing Portal (RISP) being developed by the AMRH Programme in AUDA-NEPAD should be able to extract key regulatory information from national RIMS and Regional EAC-MRH system to share at the continental level (Figure 8.5). Countries are called upon to develop their websites and make publicly available, all products recommended through the MRH process and which are granted MA in the country. To ensure effective implementation of RIMS by NRAs, the AMRH IMS TC has developed a digitilisation strategy for RIMS in Africa to guide countries as they develop their robust information management systems (Figure 8.6). It is important for all the EAC NRAs to customize this strategy and use it to develop their systems to enable interoperability of systems in the region.

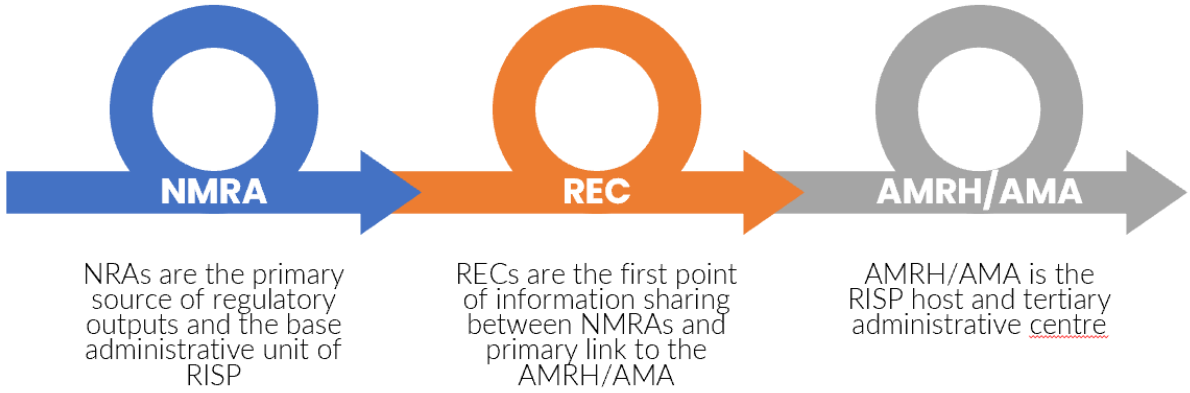
Implementation of Target Timelines by NRA

Ninety days after an application has been received by the NRA from the regional recommendation should be used as the target timeline expected by all members states to register the product. A joint recommendation should be made for the application and a joint GMP inspection conducted or GMP decision made (GMP compliance) before the clock starts. A great deal of time is usually being lost after the recommendation is made and the applicant delays submitting their application to the NRA of interest. Applicants should be given a target timeline for submitting their applications to the country of interest. An example of where this practice has been implemented is the West Africa work sharing programme, where a maximum of two years is given to applicants to submit their application to the country of interest after the regional recommendation. If this does not happen within the two years, then the application will have to be re-submitted for review again at the regional level. Countries should track the progress of each application from when the application is received to when it is given a marketing authorization.

Figure 8.5 Six Strategic Priorities For RIMS

Source: AUDA-NEPAD, Digitilisation Strategy for RIMS in Africa

Figure 8.6 RISP Linkages to NMRA, RECs, AMRH/AMA



Source: AUDA-NEPAD, RISP Framework

Implement Reliance

Only Tanzania in the region has attained ML3, it is therefore imperative for the NRAs to rely on the more resourced regulatory agencies. The NRAs are called on to sign mutual recognition agreements and implement the reliance mechanisms proposed by AUDA-NEPAD, WHO and Partners. It is clear that not all countries can attain the ML3 status in the near future but could rely on the WHO listed Authorities, and the EAC-MRH work sharing Initiative. In a study to evaluate the impact of reliance in an NRA and how it improves patient access to medical products, Danks and colleagues (2023), demonstrated how through the use of an abridged review for NCEs and generics it reduced from 179 days for a full review to 91 days for an abridged review. Countries in the region are called on to domesticate continental guidelines developed by the AUDA-NEPAD Technical committees to enhance the harmonization process.

Part II: Proposed improvement to the current operating model of the EAC-MRH Initiative

Proposed centralised submissions or approvals/registrations and advocate for a legally binding framework. (Figure 8.7)

Usually, the lead agency receives applications for joint review only when the applicant has paid the application fees to two or more countries in the region. A framework should be developed

to enable a centralised regional submission and review prior to submission to the individual countries of interest for registration. Consideration should be given to using three routes/procedures for the approval of medical products in the region; that is, a fully centralised procedure, a decentralised procedure and a national procedure. In order to enable the creation of a completely centralised approach similar to that which is implemented in the European Union, it would be necessary for the region to pursue the creation of a regional legally enforceable framework. Regardless of legislative maturity or capacity, the adoption of the centralised procedure might be made mandatory for some essential medical products to provide appropriate access in all member states. Another advantage of a centralized process is the use of local specialists in central safety monitoring and the assessment of complex items. (Figure 8.7)

GMP Inspections

Applicants have two routes to use for GMP inspection either the country process or the joint inspection process. Some delays with GMP are caused because applicants have not paid the joint GMP inspection fees. Sometimes they go back to the country and pay the GMP inspection fees and then the country will initiate the GMP process. Ideally, products that are jointly reviewed should be jointly inspected. There are cases where manufacturers or applicants do not submit an application for GMP because the GMP audit is still valid or compliant and have been inspected by two or three well-resourced NRAs such as the TMDA, PPB, or NDA. In such cases, the GMP TWG will review the reports of these NRAs that have inspected the site and consolidate the report and then make a recommendation. The GMP lead NRA for GMP is the NDA and should continue to be pragmatic in combining joint GMP and country processes. It is important to combine regional GMP decisions with the national decision. A document review should be encouraged especially as the resources are minimal and the SoPs need to be drafted by the technical team.

Reliance and Review Model

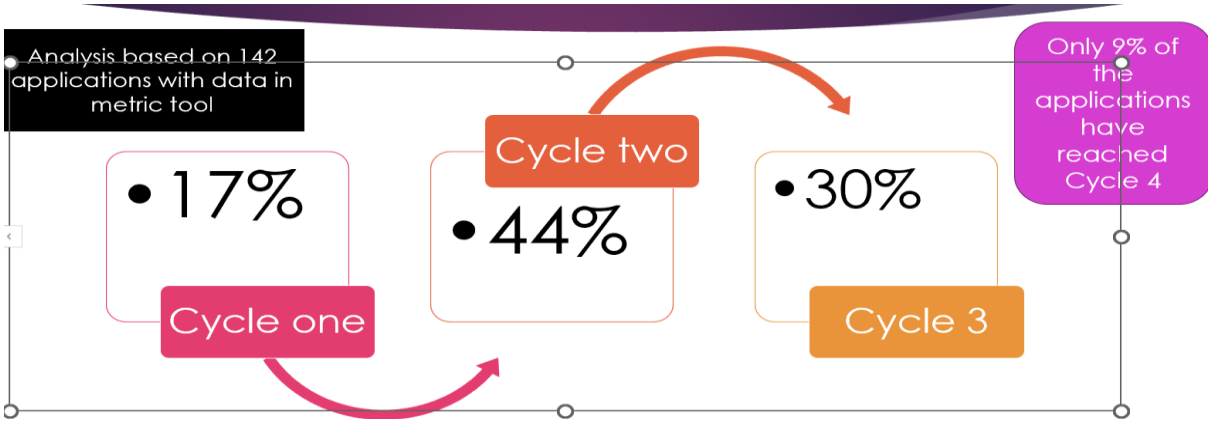
Reliance mechanisms should be implemented both at the regional and national levels. For GMP inspections, decisions should be made on a manufacturing site by relying on the GMP inspections of well-resourced NRAs. The RECs should continue to support and advocate the strengthening of the capacity of their member states using the WHO Global Benchmarking

Tool assessments and other tools such as Optimising Efficiencies in Regulatory Agencies (OpERA) and the Quality of Decision-Making Orientation Scheme (QoDoS) to facilitate inter-country and inter-REC reliance including unilateral and mutual recognition. Inter-REC reliance should be promoted among the RECs and if one REC has recommended a product for registration, the other RECs implementing the MRH programme should also rely on this decision using an abridged or verification review process.

During a focus group discussion with the heads of agencies for the EAC, the following proposals were presented by experts as inter-reliance mechanisms that could be implemented by the East African medicines regulatory programme. According to the WHO Technical Report Series NO 1033, 2021 of Good Reliance Practices in the regulation of medical products, the following marketing authorisation pathways are suggested; a standard pathway which entails an independent decision making and complete review of the application by NRAs. This might involve using the CTD format of dossier and has a long registration timeline. The work-sharing pathway allows for possible concurrent or parallel decision-making e.g the REC Joint Assessments. In addition, this would then observe and participate in review possible in EU-Medicines for all or 'EU-M4all' formerly 'EU-Article 58" or Swissmedic Marketing Authorisation for Global Health Products. Reliance Pathways entails the decision being dependent on those made by trusted regulators, a unilateral or mutual recognition pathway, risk-based pathways, abridged review, verification of sameness review, WHO collaborative procedure (CRP), and regional reliance pathways (Zazibona, EAC, ECOWAS). Also, the EAC

Compendium developed in 2014 needs to be revised as it is now 10 years since these guidelines were developed. It is critical to ensure that the MRH initiative has a legal mandate.

Figure 8.9 Current Evaluation Process- Cycle



Source: EAC Report 2024

Set Number of Cycles for the Review Process

It is important to have only three query cycles after which the application should be re-submitted as a new application. There is a need to review the query response cycles (round of queries) and then the applications can be removed from the process. Sometimes the applicants are slow in responding to queries thereby delaying the whole review process and currently four cycles are being implemented (Figure 8.9) A guideline on time points should be developed and implemented. The NRA time points should be evaluated when all requirements for registration are available and it is important for metrics to also include only regulators time at this point so that it is clear on how long regulators take to review a product. The SOP should be reviewed in order to set the maximum amount of time.

Conduct an Analysis of the Benefits of the EAC Work Sharing

An analysis of the benefits of the EAC joint assessments process to the NRAs should be evaluated. This is a powerful way to demonstrate how the programme is improving patients' access to medical products and it also demonstrates how the programme is benefiting the NRAs. The validation and analysis of each application recommendation should be carried out at each country level. It is important to conduct stakeholder consultations in order to attract more applications. It would also be helpful to perform online webinars to attract new applicants

and to create an awareness of joint review sessions as well as prepare and share expression of interests for applicants to submit applications for the joint review. In addition, a coordinating point to engage country level to conduct a validating exercise should be implemented as this will help to have clean and accurate data on where countries are on each application that is approved.

Capacity Building and training of assessors

One recommendation is to use the WHO Competency framework to evaluate the competency of the assessors and identify the training needs. It is difficult to track the impact of the trainings offered to assessors over the years as this has not been monitored and assessors attend trainings on an ad hoc basis. Each REC-MRH should develop a list a training needs for the year which will be handed to the RCD TC of the AMRH, who will then coordinate these trainings, using existing RCOREs, as well as other training opportunities that are available**.**

Develop Website and Implement the Regulatory Information Sharing Portal (RISP)

The MRH programme should publish all recommended products on their websites and implement the AMRH RISP project that will assist them to share regulatory information and knowledge exchange on the continent. An Electronic Document Management System (EDMS) is being developed through RISP which will also assist the RECs MRH to manage applications received and the distribution of the application to the assessors for preliminary review before the joint review meetings are organised.

As indicated in Figure 8.5, the RECs IMS will be the interphase between national and continental RIMS. It is important that the EAC-MRH develop a robust information management system that will implement the continental digitalization strategy at the REC level. The activation and updating of the EAC website to advocate for joint activities should also be implemented. The additional weaknesses and challenges found in the current operating model of the initiative, such as the lack of detailed information for applicants on procedures and the inadequate tracking and monitoring of timelines for products in the participating countries once the joint review is completed should be addressed by an investment in robust information management systems. By giving the region the authority to disclose this information for interested parties, this investment will increase process openness and

confidence. Additional research should be carried out in these areas, which will promote increased transparency and the use of metrics to increase efficiency. It is important to have a centralized online system to make it easier for the applicants to track their applications and indicate which process they wish to follow (Joint or country process). In addition, the AUDA-NEPAD, Trademark Africa and TMDA IT experts should align efforts to link the metrics used for EAC-MRH process to the RISP which is currently under development.

The EAC-MRH should improve the metrics currently being collected. Also the EAC secretiariat should recruit a Biostatistician who can continue to improve the processes for capturing the timelines and make sure what is going on is understood.

Communication with applicants

Any initiative that implements a decentralized procedure at submission that is, EAC MRH should inform both current and potential applicants of the target timelines for the joint review process and emphasize that, similar to other decentralized procedures like EMA or ACCESS, approval timelines in different countries will vary and depend on the national process.

The EAC MRH should implement the practice of publishing an expression of interest as is the situation by the ECOWAS MRH

Define Roles and Responsibilities of the EAC-MRH in the AMA era

According to the AMA Treaty, the RECs have a fundamental role to play in the regulatory ecosystem in Africa. There are three levels (national -NRA, regional -REC and continental -AMA) of this ecosystem each of which will need defined roles and responsibilities to avoid duplication. The roles of the RECs in the 3-tier medicine Regulatory system is recommended which would include; promoting collaboration within region; coordinating on-going AMRHI activities within the region; regulatory responsibilities for selected activities and support NRAs lacking capacity in identified activities; vigilance of products, especially against movement of SF products; providing guidance within region; provide link between AMA and NRAs; organising joint evaluations, inspections and other such activities; designation, promotion, strengthening, coordination, and monitoring of RCOREs; and coordinating the collection, management, storage and sharing of information on medical products including SF medical products. From the above roles and responsibilities highlighted, it is important to define a minimum functional package of structure, infrastructure, human resources, policies and

communication that would enable the EAC-MRH to be the gateway for AMA implementation. Defining a minimum package that the EAC-MRH will need to function optimally is a key recommendation from this study.

Incentives to applicants

The following incentives are recommended:

1. Implement eCTD which will enable transparency and will improve trust on maintained on both sides.
2. Advocate for governments to provide incentives such as tax for raw materials to be reduced for local manufacturers with a regulation to indicate that products produced locally and need raw materials should attract zero tarriff ..
3. Speed at which HoAs provide MA for the product with a maximum of 60 days to be used to give MA at country level.
4. Forward data at the regional level to the national level so that it can be faster for approval and attached to the recommendation and sent to the countries.
5. Establishment of a pool procurement mechanism for quality assured products

Part III: A proposed new improved model for the EAC-MRH initiative.

Based on the outcomes of this research, the key challenge identified which has negatively affected the effectiveness and efficiency of this initiative, is the lack of a centralized process for the submission and tracking of dossiers. It is therefore recommended that a centralized submission process be implemented for the EAC-MRH as a new improved model for the initiative. This will eliminate most of the challenges identified in this research and give the EAC-MRH Secretariat a legal mandate to receive and review applications. This will entail the establishment of a Regional Medicines Agency for the EAC. The review process should be simplified and predictable with proposed timelines that will make the process more attractive over the standard pathway. The guidance on using this centralized process should be the "SMART" initiative especially with the introduction of an electronic process (e-CTD). A centralized process for the payment of fees for joint reviews should be established alongside this process. Instead of having too many entry points, applicants interested to have their

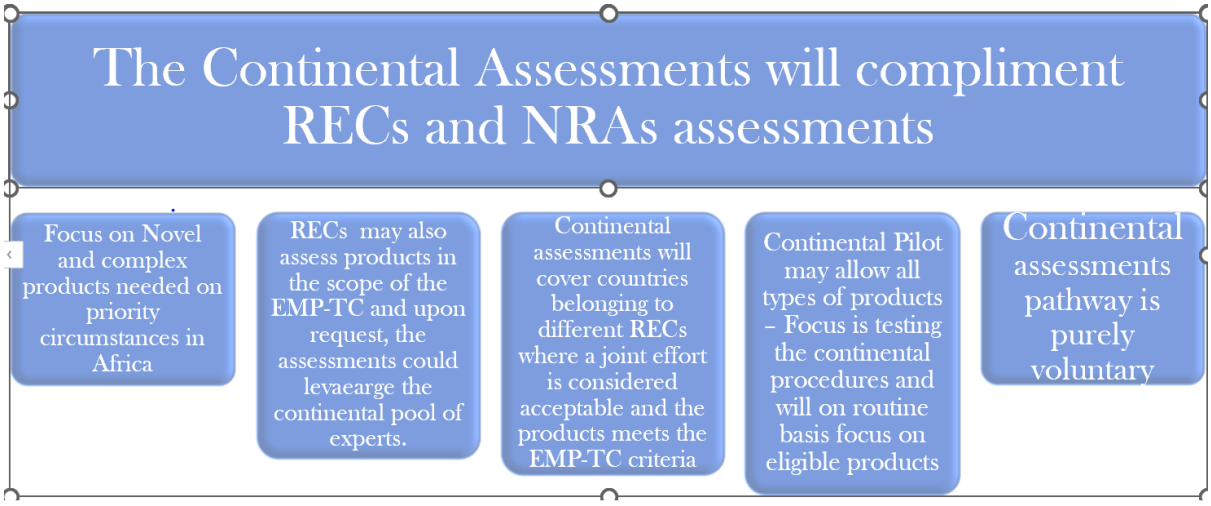
applications reviewed through the EAC-MRH should apply directly to the EAC-MRH after which the review process as per Figure 8.7 can start. Milestone one will then be the recording of the date of which the application and screening fees are received (Step 1). The centralized submission will eliminate the seven days deadline given to the countries to submit the applications they have received to the Lead Agency. Instead, screening of the application should be done within five days after receipt of the application. Screening fees should also be paid during the time of submission of the application. In Step 2, the EAC-MRH Secretariat would screen and validate the application. If there is missing information, the applicant would be notified and additional information should be submitted within five days. The EAC-MRH would then assign the application for an initial review by the 1st assessor by day 14 (Step 3).

The centralized process should have a pool of assessors with varied skills who can be called on to conduct the first and the second review of the applications for a fee (Step 4). After the application is peer reviewed by the second assessor, a joint assessment can then be planned by Day 90 (Step 5) for all assessors in the seven NRAs. If the application is a NAS or complex molecule which is not eligible for the continental process (Figure 8.8), the Evaluation of Medicinal Products technical committee can be invited to assist with the review (Figure 8.9). As clearly stated in the early chapters (Ngum et al, 2023), AMA (the continental review) will not replace but will only compliment the work of the RECs and NRAs. Other reliance mechanisms/review models should be implemented during the joint assessment of dossiers to fast track the review time. Another 90 days should be taken to complete the assessment process after the joint review to obtain additional information from the applicant. Only two rounds should be accepted for query responses. By Day 180, a final recommendation should be issued by the EAC-MRH Secretariat and confirmation letter sent to the applicant (Step 6: Figure 8.7). Within 30 days after the confirmation letter is sent to the applicant, the applicant can then submit the application to the NRA (s) of interest which will be Day 210 of the cycle (Step 7). The NRA would be expected to register or grant marketing authorisation within 90 days after receipt of the application which will be by Day 300 of the cycle (Step 8).

Figure 8.7 Priority categories for medicinal products for continental review

Source: AMRH Report 2024

Figure 8.8 The guiding Principles of the Continental (AMRH/AMA) review process

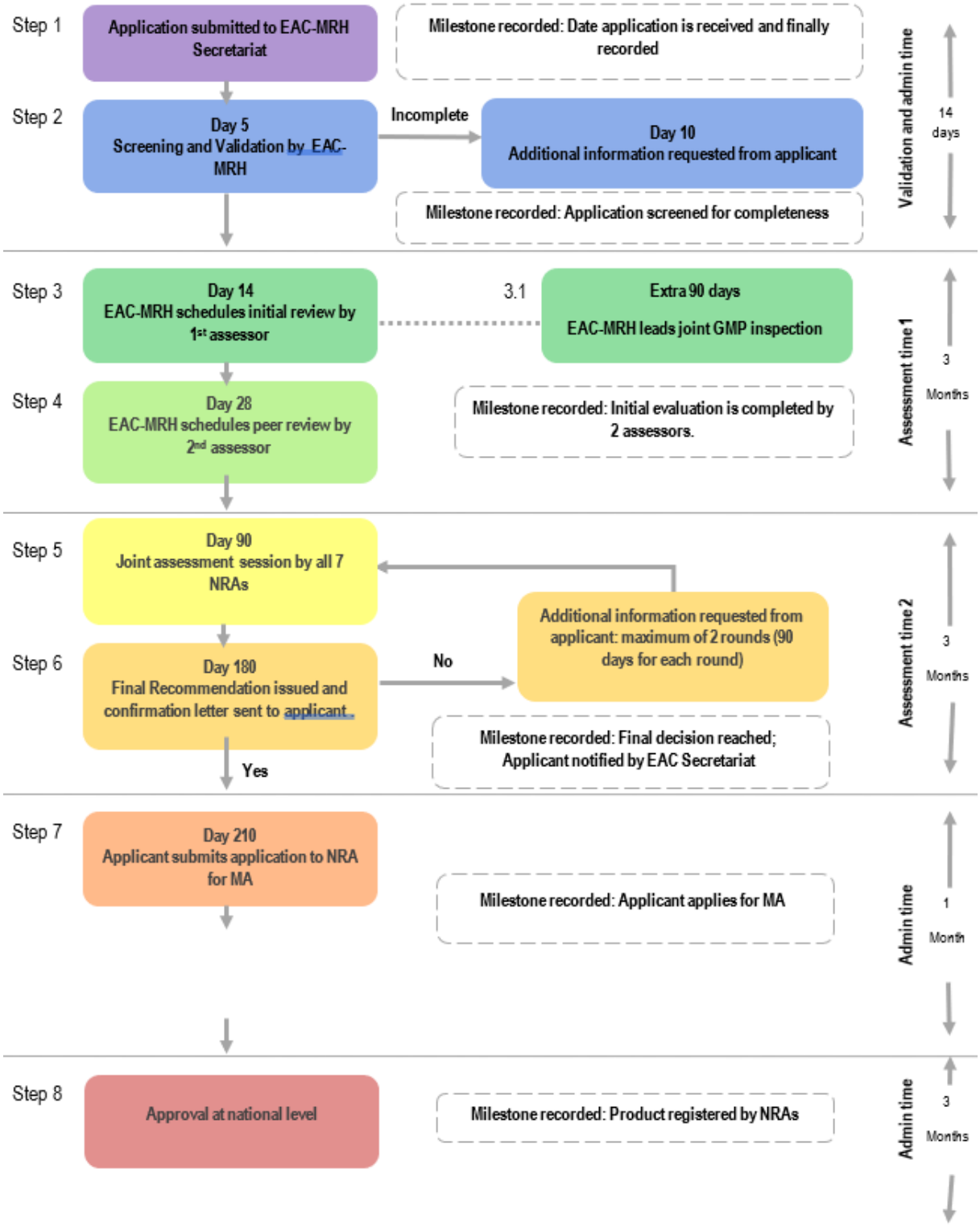


Source: AMRH Report 2024

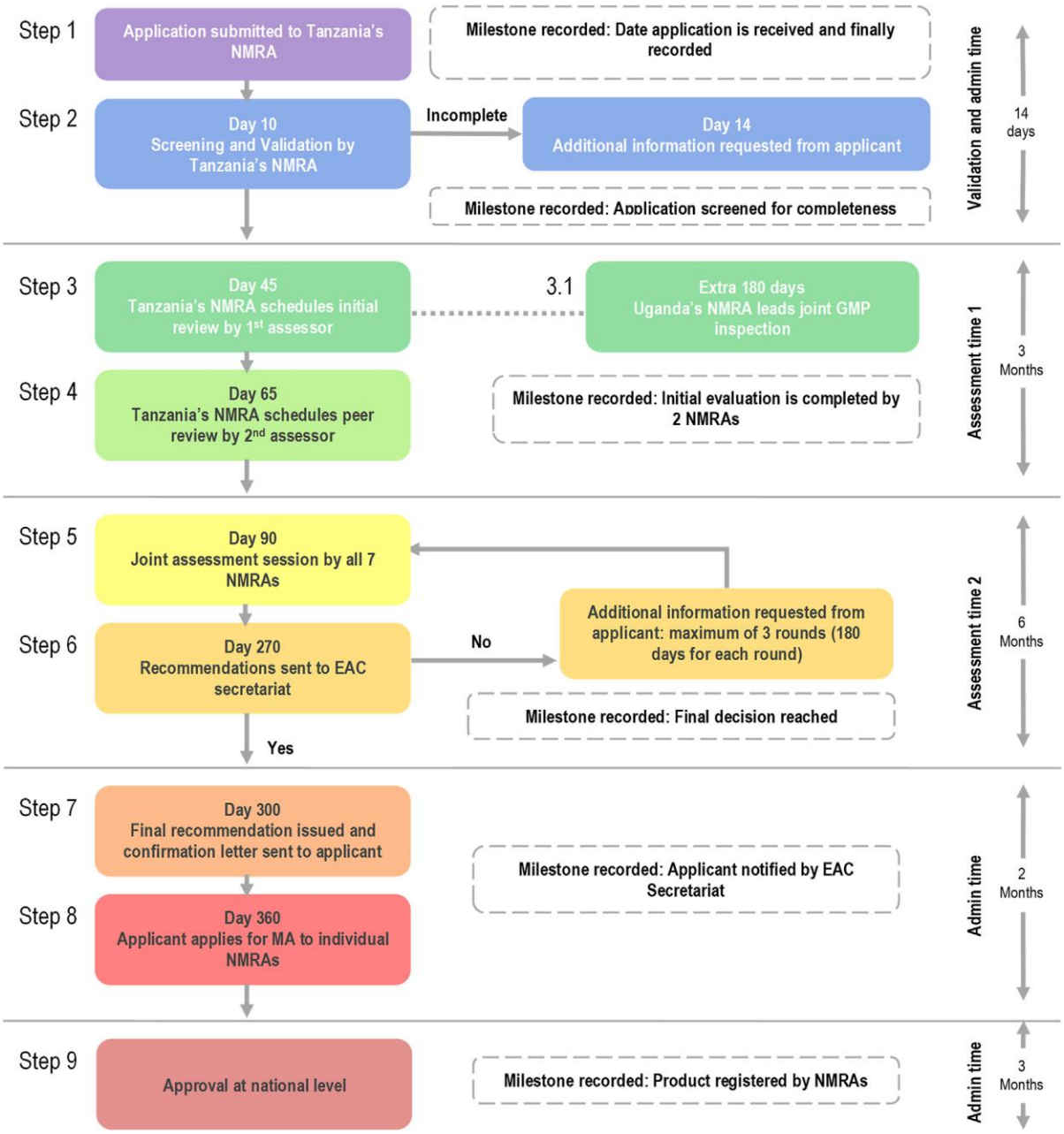
If we compare the Review process map and milestones for EAC joint assessment procedure (Figure 5.1) and the new proposed EAC-MRH centralized procedure (Figure 8.7), a significant reduction in the review timeline would be observed from when the final recommendation is issued, and confirmation letter sent to applicant by Day 180 (Figure 8.7) instead of the initial

day 300 (Figure 5.1). It is only at this stage that the EAC-MRH still has control over the application after which it is out of the EAC-MRH process and they will not have control on what the applicant does with the letter issued. The applicant could delay the submission of the application for MA to the NRA(s) or work within the given time frame of 30 days as compared to the initial 60 days allocated.

Figure 8.7 Proposed EAC-MRH centralized procedure



Review process map and milestones for EAC joint assessment procedure. (Figure 5.1)



In the current operational model of the EAC-MRH, applicants submit applications to any NRA of choice. The NRA who has received an application which is eligible for the EAC-MRH review then submits this application to the lead NRA (TMDA). The TMDA then assigns an EAC reference number to the application and the lead NRA therefore performs the screening. The centralized system will mean that the Secretariat would perform all the functions of

receiving and screening of the application (Table 8.1). However, the decentralized procedure will come in again when the applications are submitted to the first and second assessors

Table 8.1 Comparing of the current and proposed operating model

	EAC-MRH decentralized registration Initiative	EAC-MRH Centralised registration procedure
Timelines	About 360 days from receipt of application to recommendation for MA	About 180 days from receipt of application to recommendation for MA
Governing Body	EAC Heads of Agencies EAC Heads of Pharmacy Boards EAC Health Ministers	EAC Heads of Agencies EAC Heads of Pharmacy Boards EAC Health Ministers
Secretariat	EAC-MRH Secretariat with TMDA as Lead Agency for registration and Uganda as lead for GMP inspection	Regional Medicines Agency whose structure will be defined.
Process	Applications are submitted simultaneously to countries of interest leading to multiple registrations	One central submission leading to one registration
Coordination Fees	Multiple fees paid to the countries of interest	Single fee paid for screening and joint reviews and inspections
Assessors	Depend on Assessors from 7 NRAs only	Will have a pool assessor to consult with when the need arise
Technical working Groups/Expert Committees	Human Medicines	Human medicines Veterinary medicines Herbal/Complementary medicines

		Other as necessary
Scope	Following priority list medicines for managing certain medical conditions. • Medical conditions with regards to maternal, neonatal and children health o HIV, malaria, tuberculosis, reproductive and neurological disorders o Neglected diseases: leishmaniasis, pneumocystosis and toxoplasmosis, filariasis, and strongyloidiasis o Cancer, diabetes, hypertension, kidney, hepatic, and neurological conditions • Prescription Medicines from Domestic Manufacturers within the EAC region • Biotherapeutics Products and Biosimilars	All medicinal products with priority to; • Vaccines, Biotherapeutics products and Biosimilars • Medicinal products for use during emergencies, epidemics and pandemics • Medicines for management of the following medical conditions; o Relatated to maternal, neonatal and children health; o HIV, malaria, tuberculosis, reproductive and neurological disorders; o Neglected diseases, leishmaniasis, pneumocystosis and toxoplasmosis, filariasis, and strongloidaiasis o Cancer, diabetes, hypertension, Kidney, hepatic and neurological conditions Domestic Manufactured medicinal products with the EAC region.

Considerations to be made for implementation of the centralized model.

As previously mentioned, for an effective and efficient work sharing initiative, it is imperative for the EAC-MRH initiative to be institutionalized so that it can have a legal mandate to govern its activities. One of the provisions of the EAC Treaty, Chapter 21, Article 118 has already called for regional harmonisation in health (EAC Compendium, 2014). The Memorandum of Understanding that was drafted at the beginning of this project should be finalised and signed and then can be used to develop a cooperation framework amongst the countries. The sustainability plan 2023-2030 which has been discussed in depth by the EAC-MRH countries should be approved by the Sectoral Council (Ministers of Health of the EAC countries). This plan was tabled in the April 2024 Sectorial council meeting for endorsement and approval. If this sustainability plan is implemented, the EAC-MRH initiative will be self-sustainable by 2030 and will not be dependent on donor funds as has been the case to date.

CONCLUSIONS

In this plan a revised scope has been proposed with detailed indicators defined on how to measure performance. With sustainable financing, the EAC Secretariat will then be able to recruit the needed human resources and acquire the infrastructure necessary for a centralized process with a regional administrative unit hosted in the EAC Secretariat. The EAC-MRH centralized process will act as an interphase between the national and continental (AMA) review processes.

SUMMARY

- The EAC-MRH Initiative launched in 2012 has been in existence for over ten years with seven countries being members to this initiative.
- Five studies have been conducted on the EAC-MRH initiative starting with the history of the initiative, and then an evaluation and comparison of the regulatory review systems of the countries implementing the EAC-MRH Initiative was conducted. The views of both the regulators and industry was obtained on the effectiveness and efficiency of the EAC-MRH initiative. To learn from best practices, a comparison of the performance of the three regional harmonization initiatives in Africa was conducted.
- The aim of this chapter was to analyse the outcome of the studies conducted in this research and to recommend ways to address these gaps in a proposed new and improved model for the EAC-MRH Initiative.
- Using the OpERA, PEER and PEER-IND questionnaires, data was collected and analysed from NRAs and EAC-MRH for 2020 to 2023.
- The EAC-MRH Initiative can only be effective and efficient if the NRAs in the region are operating at an optimal level. Therefore, some solutions have been proposed to address the gaps identified in regulatory review processes of the EAC NRAs.
- Solutions to address the challenges of the current EAC work sharing initiative have also been proposed to improve effectiveness and efficiency.
- Finally, a centralized submission and tracking process has been proposed as the new and improved model for the EAC-MRH Initiative.

CHAPTER 9

GENERAL DISCUSSION

INTRODUCTION

According to the WHO Global Benchmarking assessment, only five out of 55 countries in Africa have a stable, well-functioning, and integrated regulatory system having attained maturity level (ML 3) and these are Tanzania, Nigeria, Ghana, Egypt and South Africa. (Khadem et al, 2020). These constrains in capacity has led to long registration times thereby hindering rapid access of medical products to patients and this has increased the availability of substandard and falsified medical products in the African Continent (Ndomondo- Sigonda et al, 2017). To address these challenges, the harmonisation of medicines regulation has therefore been implemented to address some of these challenges in medicines regulation and ensure that African people have access to essential medical products and technologies.

In 2009 the African Medicines Regulatory Harmonisation (AMRH) Initiative was established as it was recognised that during this period, through harmonisation, complexities in registration of medicines would be minimised and would therefore serve as an incentive for manufacturing companies to register their products in Africa. It was underscored that resource pooling, work sharing, and reliance would minimize duplication and would subsequently lead to the faster registration of medicines (Silo et al, 2020). Through the AMRH Initiative, five regional harmonization programmes in the East African Community (EAC), Economic Community of West African States (ECOWAS), Economic Community of Central African States (ECCAS), Intergovernmental Authority on Development (IGAD), and the Southern African Development Community (SADC) were established to facilitate the implementation of the medicines regulatory harmonization initiative in Africa. These regional harmonization programmes are all operating at different levels with about 85% of countries in Africa implementing the AMRH Initiative which serves as the foundation for the African Medicines Agency (AMA) Ndomondo-Sigonda et al, 2017, Ndomondo-Sigonda et al, 2018, Ndomondo-Sigonda et al, 2020, Ndomondo-Sigonda et al, 2021).

Some studies conducted on the EAC-MRH initiative including a special collection in *Plos* Medicines have given an overview of the implementation of this initiative (Ndomondo-Sigonda et al, 2020), its progress and lessons learnt during the first eight years (Mashingia et al, 2020), including the genesis of the East African Community's Medicines Regulatory

Harmonization initiative (Silo et al, 2020), as well as a two years roadmap by Arik and Colleagues, 2020. However, a recent evaluation on the regulatory review systems and the operating models of the EAC-MRH has not been conducted. The aim of this research was therefore to assess the regulatory review systems in the EAC with the goal of improving the review process and patient's access to medicines.

To achieve the objectives of this research, five studies have been conducted starting with a systematic search and narrative literature review which was conducted to obtain the history of the EAC-MRH initiative, its objectives, scope, progress to date and its potential contribution to the newly established African Medicines Agency (Chapter 1). This was followed by an evaluation of the review processes of the national regulatory agencies in the EAC region where a validated established questionnaire, Optimising Efficiencies in Regulatory Agencies (OPERA) was used to evaluate and make a comparison of the countries participating in the EAC joint assessment both in terms of their organizational structure, the key milestones in the review process, as well as Good Review Practices and Quality Decision-making Practices (Study 1, Chapter 3). The second study (Study 2, Chapter 4) which was also to evaluate the review processes of these agencies focused on the review models for scientific assessment as well as data requirements and approval timelines of those agencies participating in the East African Medicine Regulatory Harmonisation Initiative. An evaluation of the effectiveness and efficiency of the EAC-MRH Initiative by the regulatory agencies (Study 3, chapter 5) and pharmaceutical companies (Study 4, Chapter 6) was then carried out. This research programme concluded with a comparison of the outcome of this study with the Southern African Community Regional Initiative (ZaZiBoNa) and the West African Community (WAC)-MRH initiative (Study 5, Chapter 7).

RESEARCH OUTCOMES AND CONTRIBUTIONS

Studies that have been conducted on the EAC-MRH regarding the review model as well as the successes and challenges have mostly focused on the first phase of the implementation of the programme (Mashingia et al, 2020). With the coming into force of the AMA Treaty in 2021, the implementation approach of the regional initiatives needs to change to accommodate and support the operationalization of the AMA. This research covers the first ten years of

implementation of EAC-MRH (2012 to 2023) and is the first to have conducted a formal evaluation of the regulatory review process and operating model.

In Chapter 1 of this research, through literature review a detailed overview of medicines regulation in Africa is given with a focus on the history of the EAC, its benefits and challenges and its potential value to the African Medicines Agency. The challenges identified in this study ranged from the absence of a legal framework to support the operations of the initiative, resource and capacity constraints, inconsistences in regulatory processes and variable technical standards and guidelines between countries that do not meet international standards, a lack of tracking systems to monitor timelines, a lack of capacity and review templates for new active substances, and a reluctance from manufacturers of medical products to register their products in African markets.

In Chapter 3, the evaluation of the review processes of the national regulatory agencies in the EAC region was then conducted to evaluate and compare the implementation of Good Review Practices (GRePs) of the countries participating in the EAC joint assessment in terms of organisation of the regulatory authorities, the key milestones in the review process, Good Review Practices as well as Quality Decision-making Practices. The results of this study demonstrated how the population and size of the regulatory agencies in the seven countries in the region vary with respect to governance, four of the countries have semi-autonomous agencies while three have autonomous agencies. On the source of funding, the Burundi and South Sudan agencies were fully funded by their governments, however, Kenya and Uganda agencies are funded entirely from fees, while Rwanda, Tanzania and Zanzibar were partially funded from different sources. All the six agencies, apart from South Sudan which does not receive or review applications, had backlogs. The fees charged by the agencies varied based on the different kind of application categories received (New chemical Substances, biologicals, and generics). The key milestones for standardized regulatory processes are implemented in all the agencies with some differences identified. Queue times are different; ranging from a few weeks in some agencies to about one year in others. Three of the agencies use internal technical agency staff for scientific assessments while three use both internal and external experts for the primary scientific assessments. The clock stop time varies from agency to agency. Target timelines for the start and finish for the review committee vary from one day (Tanzania), and

one month (Uganda) to three months (Burundi) although Kenya does not have a target timeline for the committee. All the agencies are implementing some best practices on quality measures, transparency and communication. Some have activities for transparency improvement but with minimal attention to training and education. Most of the agencies have some measures in place for quality decision-making practices. One of the key challenges observed in this study is the recording of the timelines for each milestones achieved. These all vary amongst the NRAs in the region with most agencies not implementing a routine recording of timelines for key indicators such as timelines for validation, start of scientific assessment, response to questions to applicants, finalising scientific assessment and date of registration. A recommendation to address the gaps from this study was indicated for the Agencies in the EAC-MRH initiative to implement systems that will enhance the measurement and monitoring of timelines for the key milestones of the registration process such as dates of submission, validation, start of scientific assessment, as well as completion of scientific assessment and registration.

In Chapter 4, the evaluation of the review processes of the seven agencies focused on the review models and approval timelines of these agencies participating in the East African Medicine Regulatory Harmonisation Initiative in terms of the review models used for scientific assessments and data requirements. Most applications received by all countries were for generics except for Kenya that received a significant number of NAS applications (55 and 53 applications) in 2020 and 2021 respectively. Mean approval times for generics using full review varied with Tanzania's time declining for the three years to 202 calendar days in 2020, 93 days in 2022 and 61 days in 2022. Target timelines for full review for the five countries ranged between 180 calendar days (Tanzania) to the highest 330 days (Zanzibar). The three countries (Kenya, Rwanda and Uganda) utilising the verification review model, had a target timeline of 90 days while all six agencies conducted abridged reviews. The six NRAs also conducted fast-track assessments through a priority review track. The common technical document (CTD) format was mandatory for applications in all agencies. The targets for key milestones in the review process varied for each country with a few similarities. To address the gaps identified, the study recommended that all the agencies participating in the EAC-MRH initiative should consider formally recognizing the EAC-MRH as a reference agency for a reliance pathway. Other facilitated pathways should also be used for the review of New Active substances.

For the agencies to utilize and recognize the EAC-MRH as a reference agency it is critical to understand the perspectives/views of these agencies on the EAC-MRH. From the above recommendations another study to obtain the views of the EAC regulatory agencies on the effectiveness and efficiency of the EAC-MRH Initiative was then conducted (Chapter 5). Successes and challenges identified and ways to improve the initiative were also proposed. Work sharing, capacity building of assessors, reduction in approval timelines for medicines, information sharing amongst regulators were highlighted as some of the benefits of the initiative. The lack of a centralised submission and tracking system; inadequate human resources, manufacturers' failure to submit the exact same dossier to all countries of interest; lack of an integrated information management system; a lack of information on NRA or EAC websites; as well as constrains in monitoring and tracking assessment reports were some of the key challenges identified that have hindered the effectiveness and efficiency of the EAC-MRH. A regional coordination mechanism, with a central point for submission and payment of fees as well as a robust information management system to track submissions was recommended as measures to improve the effectiveness and efficiency of the EAC-MRH. Another key recommendation was that a similar study should be conducted to obtain the views of pharmaceutical companies on the EAC work sharing initiative.

An evaluation of the effectiveness and efficiency of the EAC-MRH Initiative by the pharmaceutical industry was then conducted (Chapter 6). According to the pharmaceutical companies that have used the EAC-MRH initiative, harmonisation of registration requirements across the EAC region is a very beneficial programme as this has led one registration for all countries in the region thereby reducing the workload for both assessors and applicants. The programme has also led to shorter timelines for granting pharmaceutical companies access to several markets at once, a lack of information about the process, a lack of centralised submission and tracking process and a lack of mandated central registration were some of the challenges noted by the applicants. The establishment of a regional administrative body to centrally receive and track EAC applications and the eventual establishment of a Regional EAC Medicines Authority was a strategy proposed again as the way forward. Comparing the successes and learning lessons from the other regional harmonization initiatives was then recommended as another strategy for improvement of the EAC-MRH.

A comparison of the outcome of this study with the Southern African Community Regional Initiative (ZaZiBoNa) and the West African Community (WAC)-MRH initiative (Chapter 7) was then conducted. Most respondents stated that AMRH contributed to the strengthening of regulatory systems and harmonising regulatory requirements across economic regions of Africa, potentially resulting in improved access to quality-assured medicines. Although established at different times and at the discretion of each region, the marketing authorisation application review processes are largely similar, with few differences noted in the eligibility and submission requirements, the type of procedures employed and the timelines and fees payable. The challenges identified in the three regions are also similar, with the most noteworthy being the lack of a binding legal framework for regional approvals.

STUDY LIMITATIONS

The scope of this research was limited to the review processes, milestones in the review process, review models and timelines. The study lacked the review of the input and output of these processes. The quality of these reviews was also not part of the study as well as the standard operating processes, standardised templates and reports, and the quality of the actual evaluations carried out, including whether or not they incorporate a benefit-risk assessment. Furthermore, although the EAC-MRH, and all the regulatory agencies stated that they adhered to Quality Decision-making Principles, and the use of these standards was not assessed using a structured, systematic method.

In Chapter 3 and 4, the review process focused on the key milestones achieved and the timelines used and this did not differentiate the exact timeline used for scientific review. The performance metric only focused on the information that was recorded and any information not recorded was not accounted for. The focus was more on the date of receipt of the application and the date the application was approved. How long it took for the validation process, scientific review, time taken by applicant to respond to queries was not measured. The metrics also only focused on registered products but not on applications that were registered or withdrawn. Although responses were received from all the seven agencies, most of the information was incomplete as most of the countries do not have adequate tracking systems to capture these metrices. There were several inconsistencies in the number of products reviewed during specific timelines and some products could be the backlog from the previous years.

The actual scientific review process of the EAC-MRH joint reviews and inspections was not conducted to determine the Good Review Practices implemented and how quality decisions practices are adhered to at the regional level. The review models employed during this joint work was also not determined. Information on how long it takes for countries to register the product after a regional recommendation is made was also not determined. How the products registered are available to patients was not evaluated in terms of affordability (pricing).

FUTURE WORK

Country Assessments

It is critical to conduct an assessment to understand why countries take so long to register products after a regional recommendation has been made. Another improvement of the metrics tool should be to follow up on each product throughout the review life cycle from when the application is submitted in the country for approval and the granting of marketing authorization after the regional recommendation. At the country level, the focus of this research was on the review processes of the regulatory agencies. Future research should now focus on the quality of the scientific reviews conducted by the agencies.

Assessment of EAC-MRH

Future research should be to examine the quality of the actual assessments performed during the joint reviews and GMP inspections as this research only evaluated the review process of the EAC-MRH work sharing initiative. Another improvement of the metrics tool at the regional level should be to follow up each product throughout the life cycle (from when the application is submitted by the applicant up to when it has been recommended to the countries for marketing authorization.

Regional Harmonisation Initiatives

Given that a comparison was only made with ECOWAS and SADC and the harmonization is implemented in the five regions, it will be worthwhile to conduct a similar study with the IGAD-MRH and ECCAS-MRH programmes to also identify opportunities for improvement. This will enable the AMA to have a full continental view on the gaps on the regulatory harmonization landscape on the continent. It will also be helpful to use the questionnaires from

the study 1 and 2 (Chapter 3 and 4) and Study 3 and 4 (Chapter 5 and 6) to replicate a similar study in the regulatory agencies in these two regions. This would also assist them to implement Good Review Practices, develop metrics tools and implement transparency.

Pricing and pool procurement

Another interesting study would be to track how these products are available to patients would be to understand the pricing mechanisms for these products and the focus could be on the ones that have been jointly reviewed. There is a drive now for countries to also pool resources to purchase some medical products and it would be interesting to understand how the regulatory agencies interphase with the central medical stores.

Reliance

It will be important to conduct a study on the reliance mechanisms implemented by the agencies in the EAC and the EAC-MRH programme as review timelines will be significantly shortened if the countries fully implement reliance.

CONCLUSIONS

The outcome of this research programme has demonstrated the benefits of the harmonization of medicines regulation initiative in Africa as a measure to strengthen regulatory systems and thereby improving patients' access to medicines. Following the challenges and strengths identified in implementing this harmonization initiative in the East African Community, a centralized submission and tracking system has been proposed as the new operating model, which would significantly improve the effectiveness and efficiency of the EAC-MRH Initiative. It is therefore hoped that the outcome of this research project will contribute to the further development of a progressive African Medicines Agency.

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APPENDICES

Appendix 1 – Full paper publications

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Regional regulatory harmonisation initiatives: Their potential contribution to the newly established African Medicines Agency

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ABSTRACT

Background: Key regulatory entities can serve as building blocks for the African Medicines Agency (AMA). The aim of this study is to demonstrate how the regional medicines regulatory harmonisation programmes could contribute to AMA's effectiveness and efficiency.
Methods: A literature search was conducted using key words to identify publications about the AMA, African Medicines Regulatory Harmonisation (AMRH) and East African Community Medicines Regulatory Harmonisation programmes (EAC-MRH) from 2009 to 2023. The EAC-MRH programme experience was used to highlight the benefits and challenges of African regulatory harmonisation.
Results: As the foundation for the AMA, the AMRH has established structures and workstreams to support its operationalisation, including 10 Technical Committees (TCs) and 5 Regional Economic Committees (RECs). Lessons learned from the EAC-MRH 10-year experience are being used to scale up regulatory harmonisation and could be of value to AMA harmonisation experience.
Conclusions: As of June 2023, 35 of 55 countries have either signed and/or ratified the AMA Treaty, whilst 20 have neither signed nor ratified it. An effective AMA will need strong National Medicines Regulatory Authorities as well as Regional programmes and it is imperative for more well-resourced countries to ratify the treaty to ensure access to essential medical products and technologies for the African people.

1. Background

One of the main functions of a medicine regulatory authority is to promote public health and protect the community from any harm (Giaquinto et al., 2020). The review of medical products by regulatory agencies is considered as one of the first steps to access to good-quality and effective medicines (Wang, 2022). Strong medicines regulatory systems and effective coordination will accelerate efforts to improve public health and ensure that African people have access to essential medical products and technologies, but there are several challenges that impede the review and registration of medical products in African countries by pharmaceutical companies (Narsai et al., 2012). African medicines regulatory systems are faced with resource and capacity constraints (Roth et al., 2018), including a lack of harmonised tools that meet international standards to collect, collate, analyse and report on harmonisation efforts results (WHO, 2010).

1.1. The need to strengthen African medicines regulatory agencies

A recent study showed that all but one (except for Sahrawi Republic) of the 55 African Union (AU) member states have national medicines regulatory authorities (NRAs) with different structures and level of functionality (Ndomondo-Sigonda et al., 2017).

Sub-Saharan African countries have inadequate capacity to regulate medicines due to fragmented legal frameworks and weak management structures and processes, as well as limited human and financial resources. This has led to a proliferation of substandard and falsified medicines (SFs) in various markets in the continent (Rägo et al., 2014). According to Ndomondo-Sigonda et al. (2020), of 46 sub-Saharan African countries, only 7% have moderately developed medicine regulatory capacity, while 63% have minimal capacities and the remaining 30% do not have a functional NRA in place (WHO, 2010). Moreover, regulatory systems in Africa may include poor inspection practices; ineffective

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licensing and product registration systems; inadequate access to quality control laboratories; and non-existent pharmacovigilance, clinical trials oversight and drug promotion control systems; with subsequent 30% product quality failure rates (WHO regional Office for World Health Organization Regional Office for Africa, 2013). Other issues include inadequate regulatory information management systems (RIMS), transparency and accountability as well as widespread conflicts of interest (Ndomondo-Sigonda et al., 2017). Hence, there is a need to strengthen medicines regulatory systems on the continent. One of the approaches is to promote harmonisation work and ensure alignment of different initiatives in the medicines regulatory space to ensure concerted efforts in tackling public health challenges and sustain Pan-African led initiatives.

1.2. Study objectives

The aim of this study is to demonstrate how regional medicines regulatory harmonisation programmes may contribute to the effectiveness and efficiency of the AMAusing the East African Community-Medicines Regulatory Harmonisation (EAC-MRH) programme as a particular example of how key African regulatory entities serve as building blocks for the AMA and will underpin this major continental initiative. It also highlights the benefits and challenges of medicines regulatory harmonisation based on the EAC-MRH experience that will facilitate an effective and efficient AMA.

2. Methods

A literature search was conducted using key words to identify publications about the AMA and AMRH from 2009 to 2023. Preference was given to peer-reviewed articles, but websites and annual reports were also included in the literature search as appropriate.

3. Results

3.1. The African medicines agency

The AMA Treaty came into force on the 5 November 2021 after the 15th instrument of ratification was deposited at the AU Commission in Addis Ababa, Ethiopia (Hwenda et al., 2022). As of June 2023, 35 countries have either signed and/or ratified the Treaty (21 ratified and deposited the instrument at the AU Commission, 2 have ratified but not deposited, 12 have signed but not ratified, 20 have neither signed nor ratified) (Health Policy Watch)

After the Africa Centers for Disease Control and Prevention (Africa CDC), the AMA is the second health agency that will enhance the capacity of states and regional economic communities (RECs) to regulate medical products to improve access to high-quality, safe and efficacious medical products on the continent. The AMA will also promote the adoption and harmonisation of medical products regulatory policies and standards, as well as provide scientific guidelines and coordinate existing regulatory harmonisation efforts in the AU-recognised RECs and regional health organisations (RHOs) (African Union, 2021).

3.1.1. AMA goals, vision, structure and operationalisation

The vision of the AMA is for African people to have access to essential medical products and technologies. Its mission is to provide leadership in creating an enabling regulatory environment for the pharmaceutical sector development in Africa (African Union, 2020). It is the role of the AMA to.

- support the growth of local pharmaceutical production, a key objective of the Pharmaceutical Manufacturing Plan for Africa and catalyse trade in support of the Africa Continental Free Trade Area;
- evaluate medical products for treatment of priority diseases as determined by the AU;
- regularly inspect, coordinate, and share information about authorised products;
- coordinate joint reviews of clinical trial applications for vaccines and the assessment of "highly complex" product dossiers such as biosimilars and coordinate joint inspections of active pharmaceutical ingredients (API) manufacturing sites;
- collaborate with RECs and NMRAs in the identification of SFs and facilitate information sharing across countries; and
- develop common standards and regulations and harmonise legislation.

The four main structures of the AMA are 1) the Conference of the States Parties (Ministers of Health in countries that have the signed and ratified the AMA Treaty; 2) the Governing Board (Heads of NMRAs in countries that have signed and ratified the AMA Treaty; 3) the Secretariat (The Director General and his/her staff); and 4) the Technical Committees (assets to the AMA).

The proposed structure of the AMA consists of a small staff that will focus on coordination of activities/administration and for the technical regulatory work, the AMA will benefit from expertise within the participating NRAs and technical experts (Fig. 1) (Ncube et al., 2021).

Since the AMA came into force, some key milestones have been achieved toward its operationalisation. The Republic of Rwanda was selected as the host country during the AU Assembly in July 2022 (Jerving, 2022; AUDA-NEPAD, 2022). In mid-2022, the first meeting of the conference of State Parties (COSP) was held and the procedural rules for the AMA COSP were developed and a Bureau elected. An extraordinary meeting of the AMA COSP was held in November 2022 to consider the Terms of Reference of the AMA Director General and nomination criteria of members of AMA Governing Board (Jerving, 2022; AMRH, 2022 Reports).

3.2. The African medicines regulatory harmonisation initiative

The African Medicines Regulatory Harmonisation (AMRH) initiative, which came into force in 2009, was established by the African Union Development Agency- New Partnership for Africa's Development (AUDA-NEPAD) with the aim of improving access to safe, effective and high-quality medical products and technologies in Africa (Chattu et al., 2021).

It was recognised that harmonisation could minimise complexities in medicines registration and therefore serve as an incentive for manufacturing companies to register their products in Africa. Harmonisation would also facilitate reliance, allowing countries to depend on each other's work when making regulatory decisions. Finally, harmonisation would minimise duplication of effort in dossier assessments and inspection of manufacturing sites and especially would optimise the use of regulatory financial and human resources, eventually leading to the faster registration of medicines (Sillo et al., 2020).

The AMRH initiative is the foundation for the establishment of the AMA, as the AMA will build on the successes of AMRH through regulatory systems strengthening and harmonisation in Africa. The AU Executive Council decision in January 2015, EX.CL/Dec.857 (XXVI) recognised the need to strengthen capacity of medical products regulation in Africa and the harmonisation of regulatory systems, as a foundation for the establishment of a single medicine regulatory agency in Africa, within the context of the AMRH initiative, and as part of the Pharmaceutical Manufacturing Plan for Africa (PMPA) Policy Framework (Ndomondo-Sigonda et al., 2020a). While the initial focus of AMRH is on harmonisation of processes and technical requirements for registration of generic medicines, the goal is to expand the scope to cover all regulatory functions and products, while transitioning into the establishment of the AMA.

This includes activities such as pharmacovigilance, clinical trials oversight and registration of vaccines, medical devices, and diagnostics among others, depending on identified needs. The AMRH Partners are

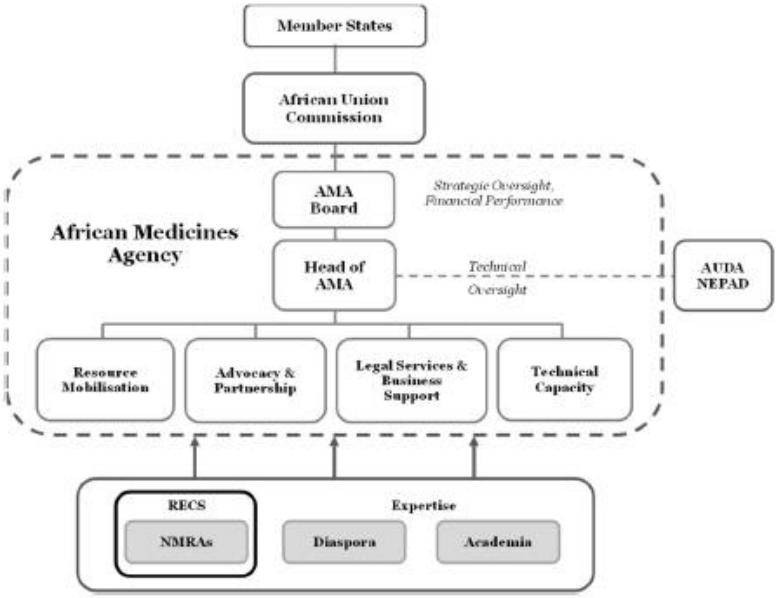

Fig. 1. Proposed governance structure of the AMA; reprinted from Ncube et al. (2021).

committed to mobilise the needed political support, including financial and technical resources to advance regulatory systems strengthening and harmonisation across the continent.

3.2.1. AMRH technical committees

As part of the alignment of regulatory systems strengthening, harmonisation efforts and networks across the continent, the AMRH has ten continental technical committees (TCs) (Fig. 2). They include the African Medicines Quality Forum (AMQF) on quality assurance and post-marketing surveillance; the African Medical Devices Forum (AMDF); the African Vaccines Regulatory Forum (AVAREF) for clinical trials and ethics oversight; Pharmacovigilance (PV); the African Blood

1	The African Vaccines Regulatory **(AVAREF)** Forum	6	Good Manufacturing Practice **(GMP)**
	Regulatory oversight on clinical trials and joint reviews of complex products including vaccines		Inspection of manufacturing sites
2	The African Medicines Quality Forum **(AMQF)**	7	Regulatory Capacity Development **(RCD)**
	Quality control and market surveillance		Coordination of regional centres of regulatory excellence (RCOREs)*
3	The African Blood Regulatory Forum **(ABRF)**	8	Medicines Policy and Regulatory Reforms **(MPRR)**
	Technical oversight on blood and blood products regulation		Domestication of AU Model Law on Medical Products Regulation
4	The African Vaccines Medical Devices Forum **(AMDF)**	9	Information Management Systems **(IMS)**
	Technical oversight on medical devices and in vitro diagnostics regulation		Support the operationalization or regulatory information management systems (RIMS)
5	Pharmacovigilance / Safety Surveillance **(AU-3S)**	10	Evaluation of Medicinal Products**(EMP)**
	Safety monitoring of medical products		Supporting joint reviews and marketing authorization

Fig. 2. AMRH Technical Committees.

Regulators Forum (ABRF); Medicines Policy and Regulatory Reforms (MPRR); Regulatory Capacity Development (RCD) Good Manufacturing Practice (GMP); Evaluation of Medicinal Products (EMP) and Information Management System (IMS). Each TC is composed of regulatory experts from NRAs in Africa who represent their REC as well as collaborative partners.

3.2.2. Regional Economic Communities

The AMRH objectives are to be achieved through harmonisation of medicines regulatory frameworks in the five regions in Africa (Chattu et al., 2021); East African Community (EAC), Economic Community of West Africa States (ECOWAS), the Economic Community of Central African States (ECCAS), Southern African Development Community (SADC), the Intergovernmental Authority for Development (IGAD).

The AMRH initiative is being implemented through the RECs, which are made up of NMRAs that belong to each region. The RECs have established Expert Working Groups (EWG) and/or Technical Working Groups and steering committees at regional levels that are supported technically and strategically by the AMRH Technical Committees and the AMRH Steering Committee, at a continental level. The AMRH Partnership Platform is a partnership of organisations contributing towards the achievement of the AMRH vision. The aim of this platform is to enhance the efficiency and effectiveness in the implementation of the regulatory systems strengthening and harmonisation agenda in Africa, through optimal coordination of the different partners and stakeholders providing regulatory oversight. The support provided by partners could either be financial, technical and/or advocacy.

Economic Community of West Africa States: Medicines are inaccessible for the majority of West Africans. This inaccessibility contributes to the persistence and spread of diseases in the ECOWAS region. Although production capacity exists in the region, most of the medicines are still imported. Launched in 2017, the objective of the West Africa Medicines Regulatory Harmonisation (WA-MRH) programme is to improve access to essential medicines, vaccines and other health products (Owusu-Asante et al., 2022). There are 15 countries in the ECOWAS region all of whom are participating in the WA-MRH programme (Benin, Burkina Faso, Cape Verde, Gambia, Ghana, Guinea, Guinea-Bissau, Ivory Coast, Liberia, Mali, Niger, Nigeria, Senegal, Sierra Leone and Togo).

The Economic Community of Central African States: All seven countries in the ECCAS are active participants in the ECCAS-MRH programme (Cameroon, Central African Republic, Chad, Congo-Brazzaville, Democratic Republic of Congo, Equatorial Guinea, Gabon). The ECCAS-MRH is being coordinated by the ECCAS body responsible for public health issues, the Coordination Organization for the Fight Against Endemics in Central Africa (OCEAC). The OCEAC leads the process of harmonising national pharmaceutical policies in Central Africa. To date, joint activities (joint reviews of marketing authorisation dossiers), training sessions and advocacy, are carried out in the ECCAS zone, in collaboration with partners.

Southern African Development Community: The SADC region is composed of 16 countries (Angola, Botswana, Comoros Islands, Democratic Republic of Congo, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Eswatini., United Republic of Tanzania, Zambia, Zimbabwe. The ZaZiBoNa initiative was created by four countries (Zambia, Zimbabwe, Botswana and Namibia) in the SADC region in 2013 to address the challenges of medicines regulation faced by NMRAs in the SADC region. These include a high backlog of applications submitted for regions in the agencies, high staff turnover, long registration timelines, inadequate financial and human resources and a lack of capacity to assess some products (Sithole et al., 2020). As of 2018, the ZaZiBoNa scheme had 11 participants from the SADC member states. These include Botswana, Democratic Republic of Congo, Mozambique, Namibia, South Africa, Zambia, Zimbabwe, Angola, Malawi, Seychelles and Eswatini. Current developments in the SADC region involve a decision to implement the SADC-MRH project using an NMRA approach. In this regard, the SADC Secretariat and Ministers in the region selected the Medicines Control Authority of Zimbabwe (MCAZ) to facilitate the implementation of the project.

The Intergovernmental Authority for Development: IGAD is composed of eight countries who all participate in the IGAD-MRH programme (Djibouti, Eritrea, Ethiopia, Kenya, Somalia, South Sudan, Sudan, Uganda). However, three of these countries (Kenya, South Sudan, and Uganda) also belong to the EAC region and participate in both programmes. The IGAD-MRH programme promotes the harmonisation of medicines registration in the region, which is a key contributor to public health and leads to the rapid access to good-quality, safe and effective medicines for priority diseases. The project is organised in sections that includes medicines registration, good manufacturing practice and quality management systems.

3.3. The EAC-MRH programme

3.3.1. History

After the establishment of the AMRH initiative in 2009, a consortium was created by African policy makers and regulators to spearhead the activities of the AMRH initiative (WHO, 2014). In 2009, the consortium decided to implement the programme with the registration of generic medicines through the African RECs (Fig. 3). The RECs were therefore requested to develop project proposals in 2010/2011. Finances from the AMRH Trust Fund were only available to support one REC and the EAC was chosen as the pilot REC for five years in 2012.

A situational analysis conducted by the AMRH Partners on the status of medicines regulation in the EAC region showed differences in countries' laws and regulations with the NMRAs of the region, such as no mutually recognised legal framework and major disparities in capacity (Kamwanja et al., 2010; Mashingia et al., 2020). To address these challenges, the EAC Secretariat in collaboration with the EAC NRAs established the EAC-MRH project as the regional coordinating body of the AMRH initiative in 2012. This was part of the implementation of one of the provisions of the EAC Treaty, Chapter 21, Article 118 on regional harmonisation in health (EAC Compendium, 2014). This was the first regional harmonisation project and the lessons learned from its pilot phase are being used to scale up regulatory harmonisation in Africa (Ndomondo-Sigonda et al., 2020a) and could be of value in the initiation of harmonisation by the AMA.

3.3.2. Challenges

AU Member States and RECs are making significant efforts to strengthen and harmonise the medicines regulatory systems by implementing programmes under the AMRH initiative (Ndomondo-Sigonda et al., 2018) despite challenges.

Legal position: The EAC-MRH initiative does not have a legal framework to support its operations. Rather than wait to establish a regional medicines agency, the member states in the region decided to rely on decisions made during the joint assessment and joint inspection activities. The reliance here by NRAs when making national decisions is based on mutual trust and respect rather than a legal framework. To keep all NRAs actively involved in this initiative, they have been assigned leadership roles based on their areas of expertise in each regulatory function ((Ndomondo-Sigonda et al., 2020). Several studies (BCG, 2017; Mashingia et al., 2020; Ncube et al., 2021) have identified that major challenges faced by EAC-MRH initiative are due to the lack of a clear legal framework by the EAC-MRH.

Resource and capacity: Resource and capacity constraints, as well as weak and fragmented legal frameworks are key challenges that have hindered the achievement of the EAC-MRH initial project objectives. There is limited technical and institutional capacity at both regional and national level (Arik et al., 2020). Different capacities of NMRAs affect trust, as sometimes the more resourced agencies tend not to trust the decisions of the newer agencies in the region; harmonisation has also limited the capacity of the less mature agencies to specialise or improve

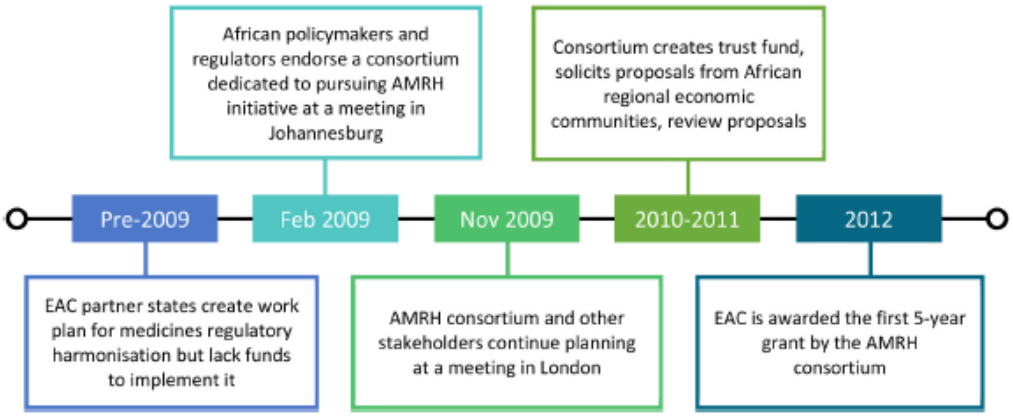

Fig. 3. Timeline of major events leading to the creation of the EAC-MRH initiative; reprinted from Sillo et al. (2020).

as they tend to rely on the mature agencies instead of building their own capacity (Mashingia et al., 2020).

Finances: A study of NMRA financial sustainability in the EAC by Ndomondo-Sigonda and associates (2020), shows that one of the major factors hindering efficient medicine regulation in the EAC is the insufficient financial resources at both the national and regional level. This study shows that the main funding source of the agencies were from industry fees, followed by government subventions and donor funds being the least. The source of funds from industry fees and government were classified as sources that will enhance financial sustainability (Ndomondo-Sigonda et al., 2020b)

Country processes: There are inconsistent regulatory processes and variable technical standards and guidelines between countries that do not meet international standards (Ncube et al., 2021). Other highlighted barriers (Mashingia et al., 2020) are a lack of a binding legal framework amongst the member states in the EAC; understaffing and high staff turnover; less involvement of the Heads of Agencies in shaping the agenda of the harmonisation project; and delays in products being registered at the national level after the regional approval has been made. Submission of applications and payment of fees by manufacturers again to NMRAs even after the joint review processes has been completed, only further delay registration timelines.

Tracking systems: A lack of transparency, especially in providing clear timelines, means that applicants are unable to track applications, NRAs and applicants are not being able to follow up on each other's questions, resulting in delays by NRAs in registering products after a joint recommendation has been made. This poor communication between assessors was also highlighted in other studies (Mashingia et al., 2020; Ngum et al., 2022.

Review templates: Despite the very high death rates in Africa due to non-communicable disease, out of the 55 countries in Africa, only South Africa has a clear framework on regulation of biosimilars (Rathore and Bhargava, 2021). The EAC-MRH still mainly focuses on the review of generics and has evaluation report, query, and screening templates for these reviews; however, it has drafted a guideline on pharmacovigilance (Mashingia et al., 2020).

Submission process: Studies also show that there is a reluctance from companies manufacturing medical products to register their products in African markets, which is also a major factor delaying access to medicines (Sillo et al., 2020). This reluctance is due to the lengthy application process and the time, expense, and effort needed for the registration process in each NMRA (Sillo et al., 2020). Another reason cited by Mashingia et al. (2020) is that manufacturers sometimes decide not to register the products in all the member states, even after a regional decision has been made.

Although three months is the target timeline for registration of recommended medical products by the NMRAs, not all products are registered in all the member states at the stipulated time for various reasons. According to the EAC joint assessment pathway, the manufacturer is expected to apply for registration of a product to NMRAs of interest after the regional decision is made. Some manufacturers may decide not to register their products in some countries and sometimes, the applicant may not be ready to market their products in a particular country (Mashingia et al., 2023).

4. Discussion

4.1. Disease burden in Africa

The African population suffers from a high disease burden (Micklesfield et al., 2022). There is a rapid increase in infectious and non-communicable disease due to the increase in urbanisation, demographics and demographic transition in Africa (Cappuccio and Miller, 2016). High disease burden has led to high morbidity and mortality in Sub-Saharan Africa (Mudie et al., 2019). This increase in disease burden is causing further strain on the healthcare systems that are not well equipped to manage such challenges (Juma et al., 2018). Corona Virus Disease (COVID-19), which became a world pandemic according to the WHO, has further exacerbated the situation (Tadesse et al., 2020). What did this mean to Africa with its very fragile health and economic systems, coupled with the already high human immunodeficiency virus, tuberculosis and malaria burden? This novel virus triggered more health and economic challenges to a continent where most of its people live below the poverty level of less than 1.9 $ a day (World Bank). One of the major health and economic challenges is access to health services due to the inability of the vulnerable population to afford medical care or quality, effective and safe medical products, as 70% of the population works in the informal sector with no health insurance and social protection (Lawson-Lartego and Cohen, 2020). This eventually leads to the people consuming sub-standard falsified medicines, which has worsened the health situation and further increased the disease burden (Amimo et al., 2020). The African continent has been exposed during the COVID 19 pandemic and thus revealing the continent's vulnerability in providing access to essential medicines, vaccines and health technologies (Sidibe et al., 2023).

4.2. Regional regulatory harmonisation initiative contribution to potential universal health coverage by AMA

One of the determinants of quality healthcare is the availability of an

"independent-science based regulation of medical products" (Sillo et al., 2020). An African continental regulatory mechanism for medical products such as the AMA is critical to address the issues of access to essential medical products on the continent. It is the hope of the African Ministers of Health, based on African Health Strategy (2016–2030) that a strong and efficient AMA will address the inequities and inequalities of health coverage as observed during the COVID-19 era and this has resulted in a call for prioritisation of continental regulation of medical products (Chattu et al., 2021).

The AMA is critical in contributing to the achievement of universal health coverage as it will enable access to quality, safe and essential medical products, and vaccines in Africa. The AMA is being established as the main driver to "enhancing regulatory oversight of medicines and vaccines across the continent's 55 countries" Chattu et al., 2021). The COVID 19 pandemic exposed the gaps and inconsistencies in medicines regulation in the 55 countries and five regional harmonisation programmes that this continental regulatory body will need to fill. In providing a service to the African people, the AMA will harmonise the regulation of medical products on the African continent (Chattu et al., 2021).

There will not be an immediate change in access to medicines, because the AMA will not replace national medicines regulatory authorities; however, experts say it has the potential to improve efficiency, reduce duplication, harmonise standards and processes to enable comparability, and encourage reliance on tested methods of medicines regulation. The agency will be helpful, as it will enforce centralised regulatory measures by bringing together all the 55 regulatory bodies on the continent. According to expert opinion (Makoni,2021), the "strength of the AMA lies in the large number of countries in the African Union, the large potential market for medicines, and the existing efforts at regional harmonisation that can be built on by the Agency". If the implementation of the African Continental Free Trade Area is accelerated, it will provide a market of over 1.3 billion people to the pharmaceutical sector. This will, therefore, address the challenge of market size that pharmaceutical companies have had for African countries and more importantly, the AMA will provide confidence in the regulatory ecosystem. This will thus increase the interest of manufacturers to invest in local production of medical products and vaccines in Africa (Sidibe et al., 2023). Therefore, improvement in regulatory science in Africa could also lead to increased local discovery and clinical trial capabilities.

The AMA will need to have strong and agile NRAs and REC-MRH programmes and or authorities to be able to address all or most of the regulatory challenges experienced for many years by Sub-Saharan Africa countries. How ready are these entities to embrace the recently established continental agency for medical products regulation?

4.3. Adoption of AMRH workstreams by the AMA

The AMA is an outcome of the AMRH initiative (Chattu et al., 2021; Ncube et al., 2021). Efforts are being made for the AMA to capitalise on the existing mechanisms that are already in place (Ncube et al., 2021). If the AMA adopts the workstreams of AMRH, then this could be a major contribution to its operationalisation, thereby speeding up the approval processes and fast-tracking the availability of medicines to patients in Africa (Chattu et al., 2021).

Through the WHO Global Benchmarking Tool (GBT), African NRAs are assessing their capacity and creating institutional development plans that will facilitate regulatory systems strengthening. According to the WHO GBT, an NRA should be able to perform some or all of the nine regulatory functions. These include: national regulatory systems registration and marketing authorization; vigilance; market surveillance and control; licensing establishments; regulatory inspection; laboratory testing; clinical trials oversight; and NRA lot release.

The GBT is a five-step approach to capacity development through which NMRAs can measure their strengths and weaknesses and then reach out for support (Broojerdi et al., 2020). The WHO recommends that countries are assessed to determine their maturity levels for each of the above functions as this is vital to understanding the capacity of the authority and the harmonisation and reliance efforts. Due to resources constraints, NMRAs with lower maturity levels can rely on countries with higher maturity levels through the harmonisation scheme as well as the good practices outlined by the WHO. Mutual recognition or cooperation agreement amongst the National Medicines Regulatory Authorities (NMRAs) is key.

4.3.1. Medicines regulatory harmonisation initiatives

Collaborations and reliance amongst countries is being facilitated by the AMRH Initiative through the regional harmonisation programs (AU Press release, 2021). In the post-COVID era, it is imperative to also strengthen regional initiatives as they work toward addressing the challenges that still prevail (Chattu et al., 2021). Given that the AMA will only regulate 5% of products, which will be considered as priority or essential medicines and complex molecules, it will not replace the NRAs or RECs but will rather complement their work. According to Article 4 of the AMA Treaty, the main objective of the AMA will be "to enhance the capacity of State Parties and RECs to regulate medical products in order to improve access to quality, safe, and efficacious medical products on the continent". Therefore, the RECs who draw expertise from NRAs will be the pillars of the AMA.

Article 30 of the AMA Treaty specifies that AMA will establish a relationship with other organisations and institutions, especially those that will assist AMA to achieve its objectives. Given that duplication needs to be minimised, the AMA will rely on the decisions of the WHO-listed regulatory authorities as well as well-resourced regulatory authorities like the EMA and US FDA as well as the WHO Prequalification.

4.3.2. Continental technical committees

The ten continental TCs established by the AMRH initiative are key to the success of the AMA, as they are already performing some AMA related functions outlined in article 6 of the AMA Treaty. Through the African Vaccines Regulatory Forum TC, the AMA can serve to unlock clinical research in Africa by enhancing the continent's contribution to clinical trials and innovation (Hwenda et al., 2022). The AVAREF is also coordinating joint reviews of applications for conducting clinical trials in Africa. The AMA can build regulatory capacity of NRAs through the eleven AMRH Regional Centres of Regulatory Excellence (RCOREs) established within the Regulatory Capacity Development TC (Chattu et al., 2021). To build capacity, a pool of regulatory experts on the continent is being established by the AMRH. This will also be one of the assets for AMA once it becomes operational. According to the AMA Treaty, enhancing optimal use of limited resources, a pool of regulatory expertise will enable capacities to strengthen networking. Also, the AMA as part of the treaty, is expected to provide technical assistance on regulatory matters to the national regulatory authorities as well as the regional initiatives. The AMA is also expected to bring technical expertise and shared financial and human resources to address the inadequate reporting of adverse effects and poor post-marketing surveillance which has led to the availability of SF medical products in the market. The pharmacovigilance and African Medicines Quality Forum TCs are already working towards addressing some of these challenges. The groundwork laid by the Evaluation and Medicinal Products TC will assist the AMA to expedite medicines' delivery on the continent and will encourage the sharing of regulatory information that will be beneficial to science (Chattu et al., 2021). This information can be shared through the Regulatory Information Sharing Portal that is currently being developed by the Information Management System TC. This portal will assist the AMA in sharing information that will facilitate the usage of the most appropriate and effective medical products in a timely manner. Information availability has been a key challenge for the harmonisation initiative (Chattu et al., 2021; Ngum et al., 2022). Another function of the AMA is to coordinate the inspection of drug manufacturing sites and this work has already commenced through the development of a

Compendium of standard operating procedures for GMP inspections for biological manufacturing facilities and other priority products and a continental reliance framework by the GMP TC.

4.4. AMA to learn lessons from the EMA best practices

It is expected that the AMA will adapt or adopt some best practices from the European Medicines Agency, which over the years has acquired a wealth of experience by spear heading the scientific evaluation of innovative and high-technology medicines developed by pharmaceutical companies for use in the European Union. Accordingly, the EMA is represented as a member of some of the AMRH technical committees. All EU member states are mandated to implement the decision from the centralised procedure. In the case of the AMA, member states are not mandated to implement the recommendations from AMA joint review outcomes. Once functional, it may be anticipated that the AMA may experience a similar delay in the registration of products due to lack of a legal mandate faced by the EAC-MRH. Similar to the EMA Committee for Medicinal Products for Human use (CHMP), the AMRH has established the Evaluation of Medicinal Products (EMP) Technical Committee as one of the workstreams that the AMA can leverage to conduct scientific assessments of complex molecules and priority products for the continent.

4.5. Boosting ratification of AMA treaty by more countries

Although the main objective of the AMA is to enhance capacity of state parties and RECs to regulate medical products to improve access to quality, safe, and efficacious medical products on the continent, universal access cannot be achieved without the inclusivity of all countries. No country must be left behind, as every human being has the right to health care despite the status of being a state party to AMA or not. It will be problematic if the AMA only serves the countries that have ratified the Treaty, as movement of SFs will continue through the porous borders (Jerving, 2022). The AUC, AUDA-NEPAD and Partners are therefore working tirelessly to encourage all the countries to ratify the AMA Treaty so that everyone in Africa can enjoy the benefit of this continental Agency. In 2020, the AUDA-NEPAD developed a country engagement plan to guide advocating for the ratification of AMA Treaty and to encourage the remaining countries to sign and ratify the AMA Treaty so that it could come into force. Currently, the guidance notes developed are being used to support NMRAs with their in-country ratification processes. Targeted workshops are being organised, especially with countries that have shown an interest and those that have well-resourced NRAs. A special envoy has also been assigned to engage political leaders of targeted countries to fast track the ratification process. All 55 countries in Africa are expected to be part of the AMA. Another approach as mentioned by Okonji (2022) to encourage more countries to ratify the AMA Treaty is to support member states, that have signed the Treaty to serve as "AMA Goodwill Ambassadors" who can inspire and advocate for the ratification of the Treaty by sharing AMA benefits at the national, regional and continental levels.

5. Conclusions

The overall benefit of the EAC-MRH program is to streamline the regulatory approach where there is one submission, one scientific review and one recommendation applicable to all partner states, with less cost to the pharmaceutical industry and regulatory authorities, including efficiency and a reduced time to marketing authorisation as well as a lack of duplication of efforts. With ten years of experience of the EAC-MRH work-sharing initiative (2012–2022), this is the right time to develop the next "Roadmap for the Future of the EAC-MRH initiative" (2023–2028) in this new African Medicine Agency era. It is hoped that the AMA will build on the successes of these regional initiatives while addressing most of the shortfalls experienced by the NRAs and the regional harmonisations programmes. If the achievements of AMRH are used as assets, then these can make a major contribution to the operationalisation of the African Medicines Agency.

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CRediT authorship contribution statement

Nancy Ngum: Conceptualization, Formal analysis, original, Writing – original draft, and reviewed the manuscript. **Margareth Ndomondo-Sigonda:** Formal analysis, and reviewed the manuscript. **Stuart Walker:** conceptualization, Formal analysis, and reviewed the manuscript. **Sam Salek:** original, Writing – original draft, outline, Formal analysis, and reviewed the manuscript.

Declaration of competing interest

The authors declare that they have no competing financial interest.

Data availability

Data will be made available on request.

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Evaluation of the Effectiveness and Efficiency of the East African Community Joint Assessment Procedure by Member Countries: The Way Forward

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Background: For almost a decade, the East African Community has implemented the Medicines Regulatory Harmonization (EAC-MRH) programme among its member states to harmonise technical requirements and standards for medical products regulation, jointly conduct scientific review of medical product dossiers to assess safety, efficacy and quality, inspect pharmaceutical manufacturing sites and streamline decision-making processes. This initiative enables the cost-effective use of limited resources and efficient and effective delivery of regulatory services to be determined, thus instilling transparency and accountability in all stakeholders, optimising the pharmaceutical market and economic development and improving access to safe, high-quality, effective medicines in the region. The aim of this study was to evaluate the effectiveness and efficiency of the current operating model of the EAC-MRH initiative, including challenges faced and to identify opportunities for improvement.

Methods: The Process Effectiveness and Efficiency Rating (PEER) questionnaire, which was used to identify the benefits, challenges, and suggestions for improving performance of EAC-MRH initiative, was completed by assessors representing seven EAC authorities in the joint assessment procedure. Semi-structured interviews were also carried out to validate the responses.

Results: This initiative has been of considerable value as it moves toward achieving its main objectives of shorter timelines for approval of medicines, information sharing among

Abbreviations: ABREMA, Burundi Food and Medicines Regulatory Authority, Republic of Burundi; AMA, African Medicines Agency; AU, African Union; DFCA, Drug and Food Control Authority, Republic of South Sudan; EAC, East African Community; FDA, Rwanda Food and Drugs Authority, Republic of Rwanda; GMP, good manufacturing practice; MRH, Medicines Regulatory Harmonization; NDA, National Drug Authority, Uganda; NRAs, National Medical Regulatory Authorities; PPB, Pharmacy and Poisons Board, Republic of Kenya; RECs, regional economic communities; SAHPRA, South African Health Products Regulatory Authority; TMDA, Tanzania Medicines and Medical Devices Authority; WHO, World Health Organization; ZMDA, Zanzibar Medicines and Medical Devices Authority, the United Republic of Tanzania.

regulators and capacity building for assessments, resulting in quicker access and increased availability of medicines for patients in the region. However, the key challenges identified that have hindered effectiveness and efficiency were the lack of a centralised submission and tracking system; inadequate human resources, manufacturers' failure to submit the exact same dossier to all countries of interest; lack of an integrated information management system; lack of information on national medical regulatory authority or EAC websites; and challenges in monitoring and tracking assessment reports.

Conclusion: The use of a robust information technology system for the central tracking of EAC products is essential to address the identified challenges and improve regulatory effectiveness and efficiency. One central point for payment is needed to expedite the process and to ensure transparency and the availability of information on decision making on national and regional websites. Other key strategies for enhancement include improving the capacity of assessors, work and information sharing and a coordination mechanism for the regional joint assessment, with the eventual establishment of a regional medicine agency.

Keywords: EAC joint assessment procedure, East African Community Medicines Regulatory Harmonization, benefits, challenges, effectiveness, efficiency, joint regulatory assessment

1 INTRODUCTION

The East African Community (EAC) is a regional inter-governmental organization of seven national medicines regulatory authorities (NRAs) consisting of six partner states, namely the Republic of Burundi, Republic of Kenya, Republic of Uganda, Republic of Rwanda, Republic of South Sudan and the United Republic of Tanzania. The United Republic of Tanzania is composed of the Tanzania Mainland and Tanzania Zanzibar. According to the EAC-MRH Secretariat 2021 report, all seven agencies have been benchmarked by WHO. One out of the seven NRAs is still working towards attaining Maturity Level 1, Four NRAs are at Maturity Level (ML) 1 and one NRA has attained ML3. All the seven agencies are at different levels of implementation of their Institutional Development Plans to improve their maturity levels. No NRA in the region currently has PIC/S membership, although the NDA of Uganda is preparing to apply for membership. No NRA has observer status in the ICH. Furthermore, TMDA, NDA, PPB, and Rwanda FDA have provided assessors for the WHO PQ medicines assessments (Copenhagen sessions). In addition, inspectors from NDA Uganda have worked under the WHO PQ Rotational Fellowship for Inspections.

Countries in this region have experienced the circulation of substandard and falsified medicines (Ndomondo-Sigonda et al., 2020). Currently, the prevalence of these products in Africa is estimated at 25%–30% and represents a major threat to public health, negatively impacting the growth of the African pharmaceutical sector and its overall contribution to economic development and resulting in numerous deaths (Ndomondo-Sigonda et al., 2020). According to Roth and colleagues, about 10% of medicines in low- and middle-income countries are substandard and falsified and the lack of timely access to good quality and effective medicines has been a major challenge in Africa (Roth et al., 2018).

The review and registration of medical products is one of the key functions of regulatory authorities that influences access to medical products (Sithole et al., 2021a). There are several bottlenecks that impact the registration of medical products in African countries by pharmaceutical companies (Narsai et al., 2012). One of these is the lack of capacity, in which 30% of NRAs do not have the necessary expertise to conduct key regulatory functions (Keyter et al., 2020a). Hence, there is a need to strengthen medicines regulatory systems in this continent.

Given the capacity differences in regulating medical products in African Member States, it is important to note that the African Union (AU) Member States and Regional Economic Communities (RECs) are making significant efforts to improve access to safe, quality, and efficacious medical products through strengthening and harmonising medicines regulatory systems. Studies show that the reluctance from companies manufacturing medical products to register their products in African markets is one of the major factors delaying access to medicines (Sillo et al., 2020). Reasons for this reluctance is due to the lengthy application process, the time, expense, and effort needed for this registration process in each NRA (Sillo et al., 2020). To improve access to safe, quality and effective medical products, the EAC joint assessment project was established in 2012, to assist in facilitating the market authorisation application process for manufacturers through a faster review of applications in the region.

A key strategy proposed by Roth and colleagues is to leverage convergence and reliance efforts (Roth et al., 2018). According to the Centre for Innovation in Regulatory Science, many NRAs are now using reliance as a mechanism to minimise duplication, maximise limited resources, build capacity and improve timely access to safe, high-quality, effective medical products (CIRS,

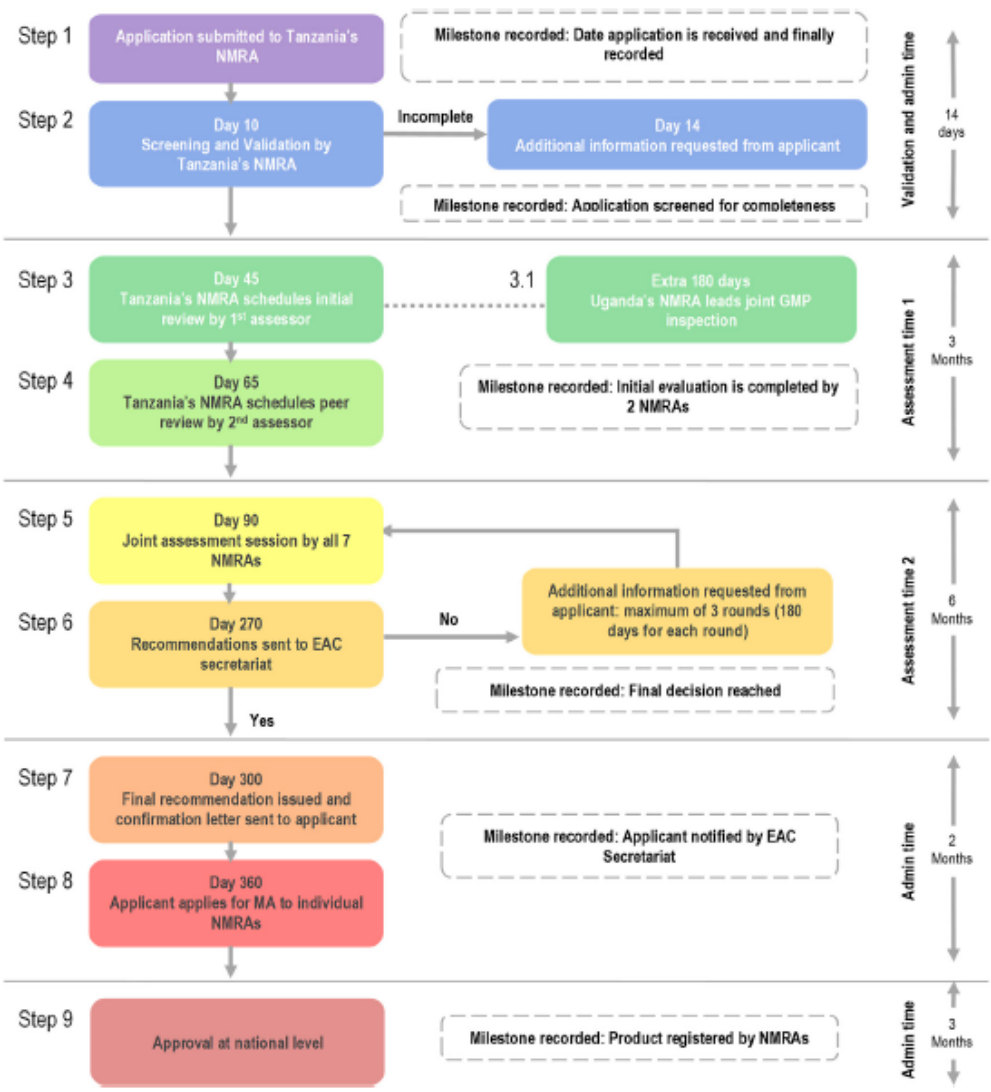

FIGURE 1 | Review process map and milestones for EAC joint assessment procedure.

2021). In their study on the impact of reliance on the review process of the South African Health Products Regulatory Authority (SAHPRA), Keyter and associates showed that the introduction of reliance pathways; that is, the use of the abridged review model by the SAHPRA, led to 68% faster timelines for the approval of medicines and improved patient access to medical products (Keyter et al., 2021).

Six authorities studied by Sithole and colleagues are using reliance (verification and abridged reviews) and this will hopefully improve access to medical products in these countries (Sithole et al., 2021a). Another comparative study of the registration process of the medicines control authority of Zimbabwe (MCAZ) with Australia, Canada, Singapore, and Switzerland indicated that reliance is key in agencies that rely mainly on industry fees for sustainability like MCAZ (Sithole et al., 2021b). These authorities are already demanding a high fee for applications for products to enter the market and do not have the opportunity to increase these fees again to support resources for regulatory reviews. On the other hand, agencies with funds from government can increase resources to improve performance. Reliance is therefore a useful mechanism to assist agencies in these instances to improve regulatory performance as they will focus their limited resources on medical products that have not been reviewed elsewhere.

However, regulatory authorities and manufacturers might not have sufficient experience in using reliance to register new medicines as it is still a relatively new concept (CIRS, 2021). Barriers and enablers in implementing reliance models identified in a study of pharmaceutical company perceptions indicated that the main strengths were shorter approval timelines and reduced requirements. In the same study, identified weaknesses of reliance included the lack of unredacted assessment reports, long submission lag times and pathways that were not fully adopted (CIRS, 2021). In addition to these challenges for reliance, a study on reliance in South Africa, identified a lack of benefit-risk assessments; the perception that reliance would lead to loss of expertise, especially in less resourced agencies; and inadequate transparency in decision-making processes as key hurdles (Keyter et al., 2020b).

The EAC joint medicines regulatory process consists of a joint assessment of dossiers of medical products and a joint inspection of manufacturing sites. This process started in 2015 and can be described using 9 steps (**Figure 1**).

Step 1 starts with the submission of the application to the lead NRA, the Tanzania Medicines and Medical Devices Authority (TMDA). In Step 2, the lead authority screens the application to check for completeness, including the good manufacturing practice (GMP) Status (Day 10). For Step 3, TMDA schedules the initial review, which also includes the GMP inspection led by the Uganda National Drug Authority (NDA; Day 45) and the GMP inspection could take another 180 days. In step 4 (day 65), an initial review is completed by two NRAs and by day 90, a joint assessment session is held (Step 5) with all representatives from the seven NRAs. At this stage a list of questions or queries are sent to the applicant when appropriate for applicant response. A maximum of three rounds is implemented, with each expected to last about 180 days. In step 6, documents are compiled and recommendations from the joint assessment are sent to the EAC Secretariat (Day 270). By day 300 (step 7), the final recommendation is issued, and a confirmation letter sent to the applicant. In step 8 (day 360), the applicant is expected to apply for marketing authorisation to individual NRAs, with approvals at national levels (step 9) and which should take place within 90 working days. Unlike the approach of the European Medicines Agency (2016) where it is mandatory for countries to register medicines approved through the centralised processed, in Africa, this is not mandatory.

With the launch of the EAC-MRH programme, the EAC authorities have made substantial progress in reducing timelines for registration of medical products using the joint review process. A study of the EAC-MRH pilot phase (2012–2017) by Mashingia and colleagues found that registration timelines were reduced from 24 months to 8–12 months for products reviewed using this process (Mashingia et al., 2020).

There has been a drive within regulatory authorities in recent years to re-engineer their processes for improved effectiveness and efficiency and this often begins with a baseline evaluation of the current process to identify strengths and weaknesses. *Effectiveness* can be defined as "doing the right thing", often measured by the value derived by customers or stakeholders of an organisation's processes or services, while *efficiency* can be defined as "doing the right things right", which saves an organisation time and resources. The aim of this study was to evaluate the effectiveness and efficiency of the current operating model of the EAC-MRH initiative, including the challenges it faces as well as identifying opportunities for improvement.

2 STUDY OBJECTIVES

1) Obtain the views of the individual medicines regulatory authorities of the EAC-MRH initiative about the performance of the joint assessment initiative to date
2) Identify the challenges experienced by individual authorities throughout the life cycle of the EAC-MRH initiative
3) Determine the strengths and weaknesses of the initiative
4) Identify the ways of improving the performance of the joint assessment initiative
5) Envisage a strategy for moving forward to improve effectiveness and efficiency

3 METHODS

3.1 Study Participants

The PEER questionnaire was completed by seven NRAs of the EAC joint assessment: Pharmacy and Poisons Board (PPB), Republic of Kenya; National Drug Authority Uganda (NDA), Republic of Uganda; Rwanda Food and Drugs Authority (Rwanda FDA), Republic of Rwanda; Burundi Food and Medicines Regulatory Authority (ABREMA), Republic of Burundi; Drug and Food Control Authority (DFCA), Republic of South Sudan; Tanzania Medicines and Medical Devices Authority (TMDA) and Zanzibar Medicines and Medical Devices Authority (ZMDA) of the United Republic of Tanzania.

3.2 Questionnaire Development and Validation

A Process Effectiveness and Efficiency Rating (PEER) questionnaire was developed by the authors to identify the views of regulators on the benefits, challenges and opportunities for improving performance of EAC-MRH initiative. The PEER questionnaire (**Supplementary Material S1**) was validated by carrying out a pilot study with two authorities to establish its practicality, applicability and content validity.

Semi-structured interviews using a checklist (**Supplementary Material S2**) were carried out with each authority to validate their responses to the questionnaire. The main respondents were the seven assessors representing their agencies in the EAC-MRH joint assessments. The Heads of the seven agencies validated the responses by the assessors. The interview provided flexibility and a further opportunity for the respondents, as they were able to give more open-ended answers to some questions. Some sections in the questionnaire were clarified, challenges in completing the questionnaire were discussed and the benefits of the study were acknowledged. To ensure confidentiality, the questionnaire was marked as "confidential" and participants were also informed

TABLE 1 | National Medicines Regulatory Authority information on human resources.

Measure	ABREMA Burundi	PPB Kenya	Rwanda FDA Rwanda	DFCA South Sudan	TMDA Tanzania	NDA Uganda	Zfdaa Zanzibar
Total number of staff in your agency	33	187	196	16	338 plus 48 temporary staff	287	150
Number of reviewers of marketing authorisation applications	8	15	15	4	50	30	10
Reviewers participating in the EAC joint assessments	4	6	4	4	19	20	5

about this during the interviews. Consent was obtained from the participants on the information that was to be shared and to minimise bias, participants reviewed the final study report. Responses and explanations were made in some sections of the questionnaire. To ensure accuracy in capturing the entire interview sessions, they were audio recorded.

4 RESULTS

For ease of understanding, the results are presented in five parts:

1) Authority resources.
2) Benefits of the EAC-MRH Initiative.
3) Challenges of the EAC-MRH Initiative.
4) Improving Performance of the work-sharing programme.
5) Strategies for moving forward.

4.1 Part 1: Authority Resources

This part of the questionnaire provided insight into the human resources availability and size of the participating NRAs.

The total number of staff for each of the seven responding agencies ranged from 33 to 338; the number of reviewers for marketing authorisation applications ranged from 4 to 50; while the number of reviewers that participate in the EAC joint assessments from these authorities ranged from 4 to 20. (**Table 1**).

Only two agencies kept a separate record of applications received for assessment under EAC-MRH while five authorities did not. Reasons given for not having such a record included inadequate capacity as well as manufacturers not filing applications in all authorities for the EAC procedure. One authority reported that although they did not have a separate record, they could use their system to filter EAC applications, as segregation of applications is possible for new applications, but the old ones must be retrieved manually as such data is not appropriately archived.

4.2 Part 2: Benefits of the EAC-MRH Initiative

This part focused on the benefits and strengths of the joint process for recommending the registration of products to NRAs, manufacturers, and patients.

Shorter timelines for approval, information sharing among regulators, and building capacity for assessments were highlighted by all seven authorities as the main benefits of the EAC initiative (**Figure 2**). Building capacity for assessments was indicated by all as a considerable benefit, which was especially apparent in less-resourced agencies. Some agencies alluded to the fact that they never had assessors before the EAC-MRH but now have been able to rectify their situation because of the EAC joint assessment process. Harmonisation of registration requirements across the region was another benefit selected by six NRAs. Leadership commitment had improved significantly because of the collaboration with EAC, World Health Organization (WHO) and NRAs.

All NRAs indicated that they have a pool of expert reviewers and this and the priority review of EAC products were the strengths of the EAC process at a country level. Regular committee meetings enabling the timely registration of products after EAC recommendation was another strength (5/7) while four NRAs indicated resource savings were a benefit.

This initiative has benefitted regulators in training, improved the performance of assessors and facilitated shared workloads, resulting in shorter timelines for approval than in individual countries. It has also provided a platform for interaction and information exchange with other regulators. However, this interaction occurs only during assessment sessions and there is no post-assessment exchange (**Figure 3**).

There is a reduced burden for applicants, who compile only one dossier (modules 2–5) for submission to multiple countries and receive the same list of questions from multiple NRAs, enabling the compilation of a single response package, leading to savings in time and resources. Shorter timelines for approval compared with that of individual countries has enabled access to various markets at the same time.

The EAC-MRH procedure has allowed quicker access to quality-assured medicines and increased the availability of medicines for patients in the region. However, this initiative has not reduced the prices of medicines, as some generic products still maintain high prices. Furthermore, because applicants do not always apply to all agencies participating in the EAC-MRH joint assessment, the benefits of the EAC initiative for patients will only apply to some NRAs in the region.

4.3 Part 3: Challenges of the EAC-MRH Initiative

The major challenge to the initiative identified by the authorities is the lack of a centralised submission and tracking system. Also, as mentioned, manufacturers may only apply to NRAs in their countries of interest.

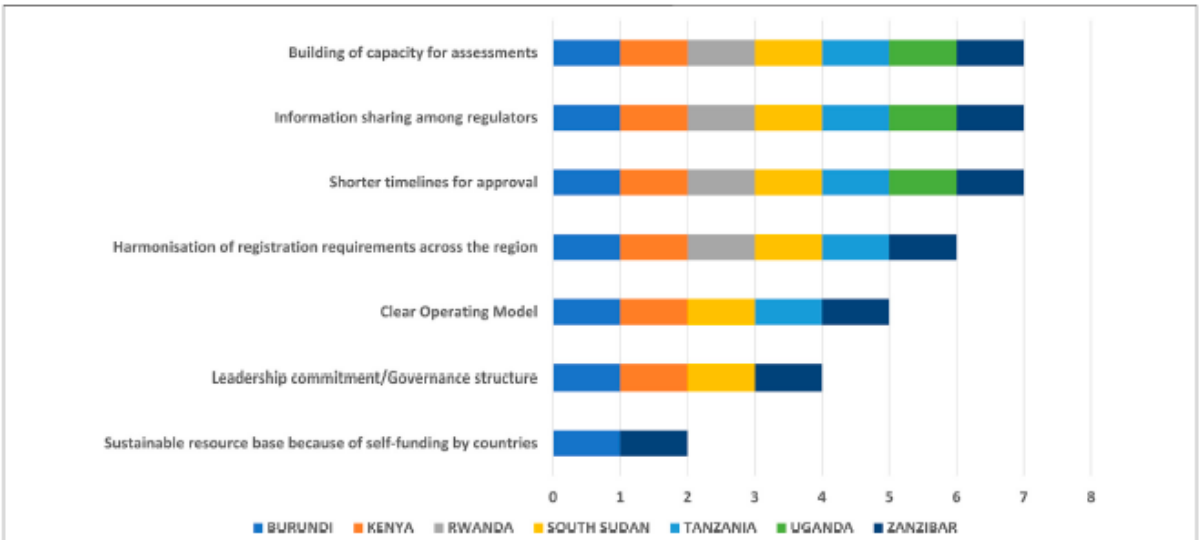

FIGURE 2 | Benefits of the EAC-MRH initiative.

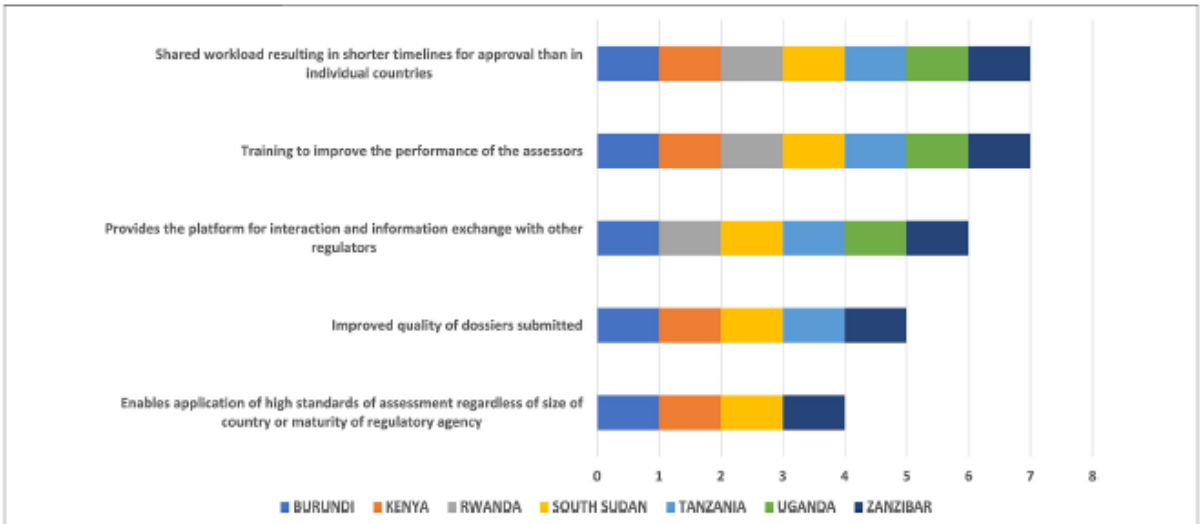

FIGURE 3 | Benefits of the EAC-MRH initiative to regulators.

The lack of detailed information on the process for applicants was expressed by four respondents, with the concern that applicants sometimes apply to both the EAC and to the NRA.

One NRA respondent indicated unequal workloads among the NRAs as a challenge, as dossiers are allocated to the well-resourced NRAs while less-resourced NRAs are given query responses from applicants to process. These assignments are necessary because new applications and complex dossiers cannot be assessed by the less resourced NRAs, but they result in an increased workload for authorities with greater resources compared with those that are less resourced.

Lack of sharing of consolidated (aggregated) information by the lead country, particularly for consolidated assessment reports was also cited as a major challenge. Assessors often struggle to get reports after the assessment sessions are completed, because, although there is an assumption that countries safely retain reports after assessment, this is not the case (**Figure 4**). Following an interview, one of the respondents stated that: "Only the list of products approved are shared without the

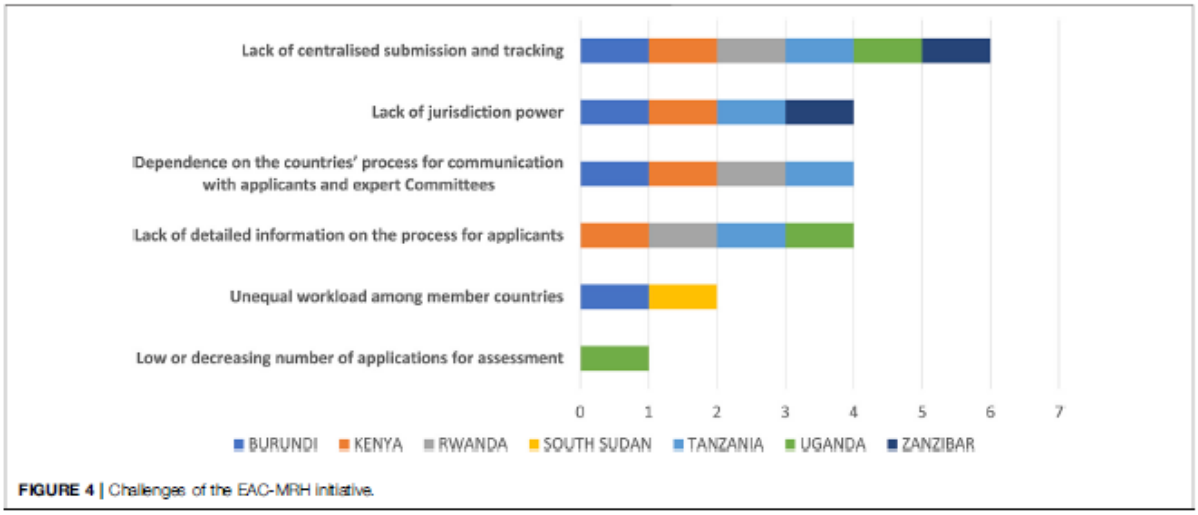

FIGURE 4 | Challenges of the EAC-MRH initiative.

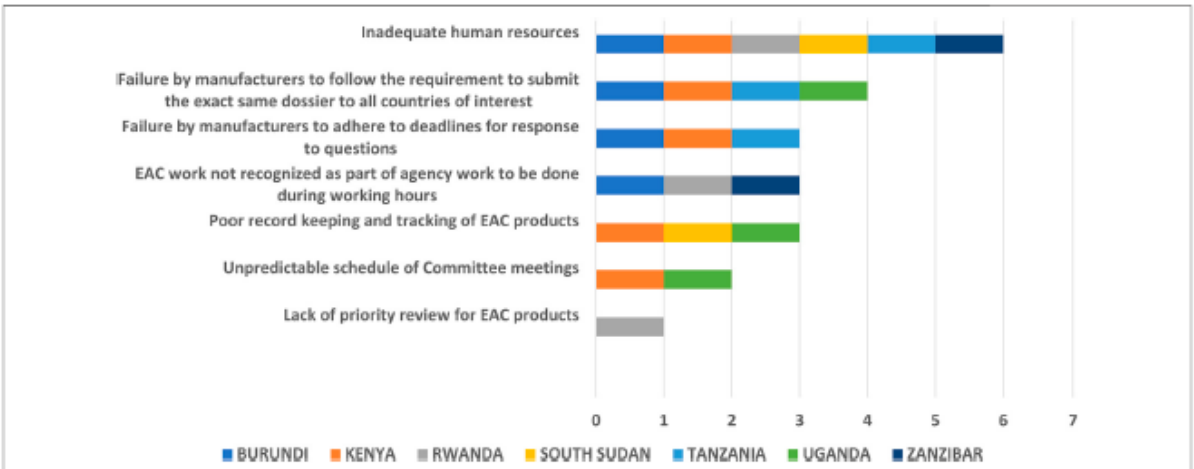

FIGURE 5 | Challenges assessing EAC-MRH products at country level.

report. This delays the process of registration in order to get the report as it is needed for national registration".

Most NRAs mentioned inadequate human resources as the key challenge at a country level and even one of the well-resourced NRAs expressed the need for more assessors to adequately handle the number of applications received for assessment.

Failure by manufacturers to follow the requirement to submit the exact same dossier to all countries of interest is also a major challenge for authorities. Poor record keeping and tracking of EAC-MRH products at national level is another hurdle for some agencies, as they do not maintain a separate record of applications received for assessment under EAC-MRH programme, and applicants sometimes submit applications for joint review to the EAC and then submit the same application at a national level. This creates duplicative communication, with parallel assessments conducted at both country and regional levels.

The unpredictability of applications causes scheduling inefficiencies, sometimes warranting the convention of unscheduled meetings to cover unanticipated applications or the postponement of scheduled meetings if enough applications have not been received.

Although the EAC-MRH work can provide learning experience to assessors, it is not recognised as part of regulatory authority work to be carried out during working hours, which was seen by authorities as an issue.

Failure by manufacturers to adhere to deadlines in response to questions is a challenge and due to this delay, some NRAs may provide marketing authorisation without the nomination of the local technical representative by the manufacturer as

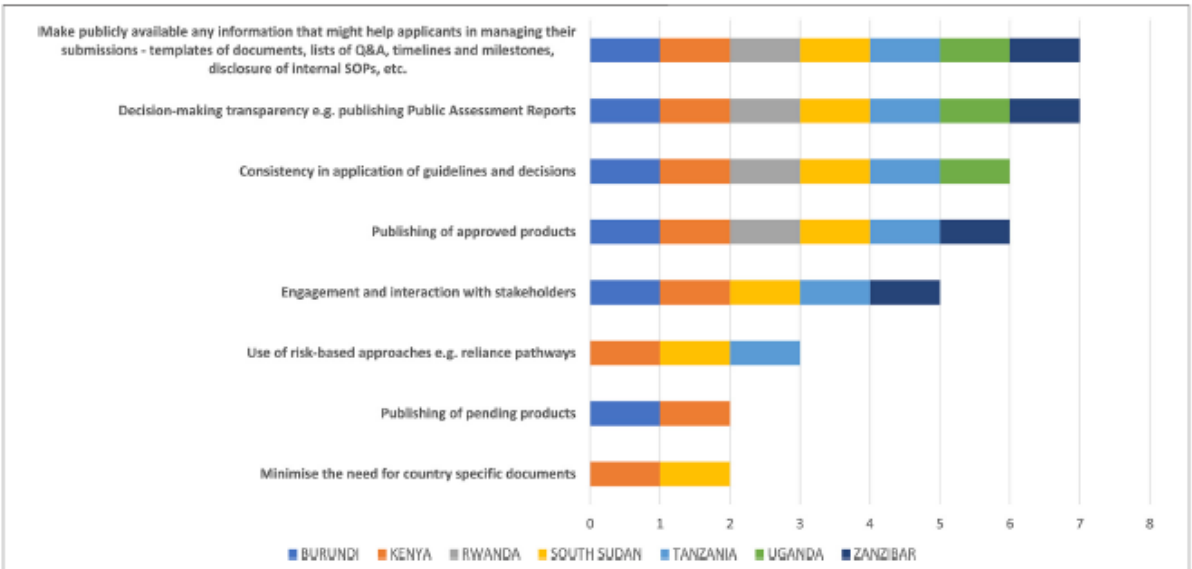

FIGURE 6 | Ways to improve effectiveness of the EAC-MRH initiative.

required (**Figure 5**). Because the EAC conducts a stringent assessment, applicants may apply to less stringent countries (NRAs) to get their products registered. However, applicants do not have full information on the application process, as there is no guidance on how to submit applications on the EAC website and there is lack of clarity about the process for submission and follow up in each NRA. Applications should go to the lead NRA for EAC assessments, but some applicants still send applications to other NRAs. There are significant differences in time to the implementation of EAC-MRH recommendations by the NRA which could be caused by the lack of a centralised system for payment of the application fees to all EAC NRAs. Finally, differing labelling requirements in participating countries was also highlighted as one of the challenges faced by applicants.

4.4 Part 4: Improving the Performance (Effectiveness and Efficiency) of the Work-Sharing Programme

Determining the views of the regulators in improving effectiveness and efficiency of the EAC-MRH initiative was an important part of this study. The top three ways to improve effectiveness identified by respondents were 1) decision-making transparency; for example, publishing public assessment reports or making any information publicly available that might help applicants in managing their submissions such as templates, lists of questions and answers, timelines and milestones; 2) disclosure of internal SOPs; and 3) consistency in application of guidelines and decisions (**Figure 6**).

Other suggestions for improvement included ensuring good record keeping for application and report traceability and sharing access to the consolidated assessment reports and query responses with NRAs by the host country NRA.

The host country for GMP should also share inspection reports with the EAC secretariat, sharing product approval letters with the focal persons. This information should be uploaded to the portals in order to facilitate compliance with NRA requirement for proof of how products are approved through the EAC procedure. This information is typically provided to the applicants, but a copy should also be requested to be sent to the NRA to assist scheduling of the final committee meetings at the national level.

The top five ways identified to improve the efficiency of the EAC initiative were (**Figure 7**) 1) improved central tracking of EAC products; 2) the use of robust IT systems; 3) compliance with target timelines by measuring and monitoring each milestone in the review process; 4) transparency on metrics and statistics and 5) a centralised system for submission of applications and communication with applicants.

4.5 Part 5: Strategies for Moving Forward

The following proposals were suggested to improve the EAC operating model. First, continue with the current operating model and establish an EAC integrated information management system to manage and process applications; second, continue with the current operating model but provide full information on the process, including timelines and milestones as well as approved products on every participating country's website and on the EAC website. The third option, to continue with the current operating model unchanged was not considered appropriate.

Other strategies proposed that would strengthen the initiative going forward were.

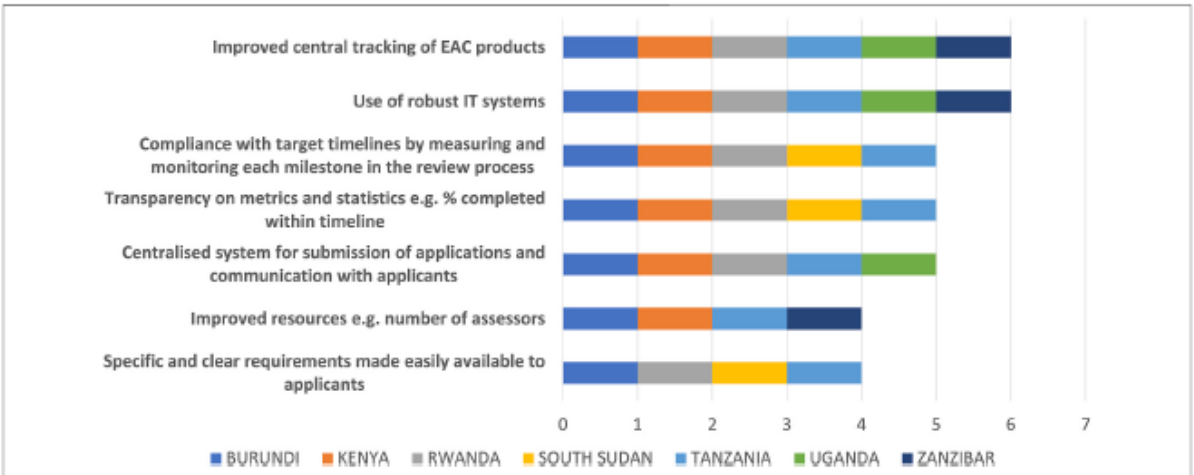

FIGURE 7 | Ways to improve efficiency of the EAC-MRH initiative.

4.5.1 Capacity Building

The EAC should support and work closely with less-resourced regulatory authorities to build their capacity to the level of better-resourced NRAs in the region. Following an interview, one of the respondents stated that: "A major request here is for the EAC to facilitate the process of weak NRAs in order to improve from the basic to the intermediate level and so they eventually become experts". The NRAs should be supervised after the joint review processes to make sure they are doing the right thing. Although the expectation is that the EAC experts are well versed with regulatory subject matters after training, this is not always the case, and supervision may still be needed. In addition, training is currently needed for new assessors as many trained experts have left their agencies. Finally, the EAC joint assessment should be included among the workload of the authority to avoid delays in the assessment process.

4.5.2 Improving Work and Information Sharing

Improved communication within the EAC NRA is critical and this can be achieved by sharing the final assessment reports of the approved products with all NRAs. Because authorities must access the reports for the national registration process, sharing only the list of approved products without the reports results in unnecessary delays. The development of a robust IT system for the EAC-MRH that can be used for tracking and uploading dossier as well as a repository for reports is required. Apart from Tanzania NRA, the agencies in the region do not have an appropriate IT infrastructure, although Kenya is in the process of developing such a system.

The availability of financial or technical support will assist the development of an efficient information management system.

4.5.3 EAC–MRH Coordinating Mechanism

The authorities agreed that the EAC-MRH coordinating mechanism at the secretariat level should be strengthened. Legal procedures should be developed to enable the EAC secretariat to perform some functions such as the collection of fees and charges for joint activities that are not currently performed by NRA such as active pharmaceutical ingredient master file certification procedures and inspection of clinical research organisations. Regularly sharing research findings, providing regulatory training, and the exchange of experts for mentorship, coaching and capacity building of EAC NRAs would be helpful. The need for all seven NRAs in the region to be operating with similar standards is an important objective for developing competency. Experience has shown that manufacturers take applications to agencies with lower standards, as they will request fewer requirements and make the process easier than the EAC process. Therefore, it is important that NRAs in the region have the same standard as the EAC-MRH process. All NRAs in the region should encourage more companies to embrace the EAC-MRH initiative.

4.5.4 Establishing a Regional Authority

Establishing a regional authority was reported to be the best strategy for improved performance, as it would promote innovation and access to new technologies; ensure all EAC NRAs have access to high-quality, safe and effective medicines; improve the quality of medicines and reduce sub-standard and falsified products in the region as well as improve regulatory expertise across the EAC; provide a global overview of the different regulatory developments at national and international levels as well as facilitating information sharing and best practices among regulatory experts.

The reasons for not establishing a regional authority cited by respondents included a need to strengthen the regulatory systems for all the EAC NRAs. As many of the authorities depend on the fees collected from the applicants to fund their operations, distributing the fees among the members states if the regional authority was established would present a challenge. It was further suggested that the region is not sufficiently mature yet for a regional agency; however, by establishing the EAC regional medicines authority, capacity building and existing collaboration among countries might be maximised. It was also stated that the establishment of EAC regional medicines authority is not

necessary as the African Medicine Agency (AMA) will soon be coming into force; however, the mandate for the AMA depends on the support of the regional agencies. It is understood that the AMA will be regulating only complex molecules while NRAs and Regional Agencies will continue with evaluation of other essential medical products. Therefore, the AMA is not replacing the NRAs, but will complement and support their work.

5 DISCUSSION

The aim of this study was to evaluate the effectiveness and efficiency of the current operating model of the East African Community Medicines Regulatory Harmonisation initiative including the challenges it faces as well as identifying opportunities for improvement.

The NRA acknowledged that the initiative has been of considerable benefit as it has moved toward achieving its main objectives, which are shorter timelines for approval of medicines, the existence of information sharing among regulators and building capacity for the agencies. The timely registration of products after EAC recommendation has been enabled by regular EAC committee meetings, shared workloads and the creation of a pool of expert reviewers, which has led to resource savings. Also, allowing applicants to compile one dossier for submission to multiple countries has enabled the industry to have simultaneous access to several markets. The strengths of this initiative have resulted in quicker access and increased availability of quality-assured medicines for patients in the region.

The median time for joint assessment in 2019 was reported to have decreased to 240 working days, demonstrating that the EAC joint assessment process was becoming more efficient (Mashingia et al., 2020). In the same study, registration timelines at the national level were reduced from 24 months to 8–14 months during the 2012–2017 time period (Mashingia et al., 2020). Giaquinto and colleagues also confirmed that one of the strengths of this initiative was the implementation of the joint assessment and work-sharing procedure with the introduction of the submission of one dossier by applicants to all EAC authorities (Giaquinto et al., 2020). The twinning programme was also identified as one of the key strengths of this initiative (Giaquinto et al., 2020).

However, several key challenges were identified that have affected the full realisation of the benefits of this initiative. They include the lack of a centralised submission and tracking system, with most agencies not having separate records of applications received for assessment under EAC-MRH, inadequate human resources, failure by manufacturers to follow the requirement to submit the exact same dossier to all countries of interest, lack of information on country or EAC websites, poor record keeping and tracking of EAC products, assessors not having access to reports after the joint assessment sessions, and the EAC-MRH work not recognised as part of the respective national authority workload.

The outcome of this study also has confirmed the findings from other authors. In a pilot study of the EAC-MRH, Mashingia and associates identified numerous challenges faced by the EAC harmonisation initiative. These included the difficulty for applicants tracking the progress of their applications as the system is not transparent in terms of timelines; inadequate follow-up to questions by both applicant and NRAs; delays in some products being granted marketing authorisation at the national level after the regional approval has been made; financial sustainability as well as submission of applications and fees by manufacturers to all EAC NRAs after the joint review process (Mashingia et al., 2020). Different capacities of NRAs affects trust, as sometimes authorities tend not to rely on the decisions of the new authorities in the region. Whilst harmonisation has had some benefits, it has impacted the less mature agencies who have not specialised, as they tend to rely on the mature agencies instead of building their own expertise. Other barriers highlighted in the study were lack of a legally binding framework amongst the NRA in the EAC; understaffing and staff turnover and less involvement by the heads of agencies in shaping the agenda of the harmonisation programme (Mashingia et al., 2020).

To address some of the weaknesses and improve effectiveness and efficiency, it is suggested that the use of a robust IT system to improve the central tracking of EAC products is essential. Ensuring the availability of information on decision-making transparency on the websites (national and regional) and establishing one central point for payment would also make the process faster. The lesson to be learned from the European Medicines Agency is that registration of medicines approved through the central process should be mandatory. With only one NRA in the region that operates at maturity level 3, improving the capacity of assessors as well as work and information sharing and the coordination mechanism for the regional joint assessment programme with the eventual establishment of the regional medicine's authority would be key strategies for moving forward. The African Medicines Agency treaty came into force on 5th November 2021 after the 15th ratification instrument was deposited at the African Union Commission. Two EAC member states have ratified the AMA treaty. One of the mechanisms being put in place to operationalise AMA is the building of regulatory work force. The African Medicines Regulatory Harmonisation Initiative has been leading the work force development through the establishment of Regional Centres of Regulatory Excellence (RCOREs) and the medicines regulatory harmonisation programmes (Ncube et al., 2021). Giaquinto and colleagues are also of the view that transparency, responding to feedback from industry, meeting registration timelines, reliance and utilising metrics would further improve access to essential medical products in the region (Giaquinto et al., 2020). Charging its own fees as the initiative increases its scope and making joint regulatory decisions mandatory would assist in sustaining the initiative (Giaquinto et al., 2020). In their study on the evaluation of the review models and approval timelines of countries participating in the Southern African Development Community Medicines Regulatory Harmonization (SADC-MRH) project, Sithole and associates recommended that national regulatory systems be strengthened to equip them to fully participate in reliance initiatives such as Zazibona (Sithole et al., 2021a). This recommendation would also apply to the EAC-MRH joint assessment procedure, as countries in this region work towards relying on the reviews and decisions made by other agencies in order to fast track access to safe, high-quality and effective medicines by patients. The opportunity to implement a reliance strategy by regulatory authorities would improve transparency and accountability and take advantage of regulatory decisions through

the utilisation of assessment reports. According to Keyter and colleagues, published assessment reports should include information on how the regulatory authority has analysed the benefits and risks of the medical product and made their final decision. The study recommends the use of a standardised approach to public assessment reports to improve communication on benefit-risk assessment, which in turn would support any reliance initiatives (Keyter et al., 2020a).

Arik and colleagues also proposed several approaches in the EAC Road Map 2020–2022 to address the challenges encountered in implementing the EAC-MRH project. These included having Regional Technical Officers, who are fully dedicated to regional activities, unlike the usual practice, in which NRA staff have had to take part on an ad hoc basis, with insufficient time allocated for regional activities, the establishment of a cooperation agreement, the introduction of a coordination fee to support regional assessments and inspections, as well as the expansion into new product areas (biologics, biosimilars) should be considered. A major proposal in the road map was the establishment of single autonomous authority for the region (Arik et al., 2020).

The key recommendations in this study to improve effectiveness and efficiency of the EAC-MRA joint assessment include:

1) Initiation of an industry cross-sectional study—A similar study should be conducted with the industry to obtain their perception of the joint assessment procedure so that there is a balanced view from both regulators and the industry.
2) Initiation of a longitudinal study–this would enable collection of efficiency and effectiveness data in order to demonstrate change (i.e., improvement) over time.
3) Measuring and monitoring timelines—The development of an integrated system for tracking applications for the regional initiative to monitor registration timelines of the products. NRAs should take full responsibility for tracking applications and recommended products for the EAC joint procedure. Also, An internal portal for information sharing by the assessors should also be made available to enhance post-assessment session interactions by regulators. This portal should also be used as a repository for reports. In addition, target timelines should be established for all the milestones including review time and applicant response time.
4) Availability of submission guidelines—The existing EAC-MRH programme and NRA websites should be enhanced with clear guidelines on the process of submission for the EAC procedure and follow up by each authority to improve the application process, transparency, accountability, and communication.
5) Training and capacity building–Continuous training of assessors should be conducted, as it would lead to staff retention and improvement in motivation, especially as there is high staff turnover within the authorities. The twinning programme should be reinstated, as it was of great benefit to the less resourced agencies.
6) The EAC-MRH coordination process–This should be strengthened to improve programme implementation and achieve the expected results. Sensitisation and awareness campaigns should be conducted to encourage manufacturers to utilise the EAC-MRH procedure. Process of payment of fees by applicants should be addressed with the establishment of one central point for payment and decision making, which would make the process faster. Dedicated full-time staff should be appointed for the assessment of regional dossiers and the sustainability of the initiative will be enhanced if more technical officers are appointed
7) Regional Medicine Authority—The EAC Secretariat should re-consider the decision to establish a Regional Medicines Agency.

6 CONCLUSION

All agencies expressed the importance of the EAC-MRH work sharing initiative, especially with the current limited resources. The relevance of this initiative in the region cannot be over-emphasised, as it has enabled the regulatory institutions in the region with limited resources to continue to fight both sub-standard and falsified medical products and technologies. With the establishment of the African Medicines Agency, there is great hope that this continental authority will help shape the regional agencies. The EAC NRAs, African Union institutions, development partners and all stakeholders should be called on to mobilise resources that can improve the effectiveness and efficiency of the EAC joint assessment procedure. According to Ndomondo-Sigonda and colleagues, the problem of substandard and falsified medical products in Sub-Saharan Africa can only be addressed if the National Medicines Regulatory Authorities have the necessary support from their national governments and the public as well as a legal mandate to manage the regulation of medical products with the necessary human and financial resources (Ndomondo-Sigonda et al., 2020). To continuously improve this work-sharing and reliance initiative, the above key recommendations would need to be implemented at both national and regional levels.

DATA AVAILABILITY STATEMENT

The dataset for this study is available upon request to the corresponding author.

ETHICS STATEMENT

The study was approved by the Health, Science, Engineering and Technology ECDA, University of Hertfordshire, United Kingdom.

AUTHOR CONTRIBUTIONS

NN: Designed the study, collected, and analysed the data and wrote the first draft of the manuscript. JM: Interpreted the results and reviewed subsequent drafts of the manuscript. MN-S: Contributed to the development of the PEER questionnaire and reviewed subsequent drafts of the manuscript. SS: Designed the study, interpreted the results, and reviewed subsequent drafts of the manuscript. SW: Designed the study, interpreted the results, and reviewed subsequent drafts of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.891506/full#supplementary-material

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Evaluation of the effectiveness and efficiency of the East African community joint assessment procedure by pharmaceutical companies: Opportunities for improvement

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Background: A 2021 study to determine the viewpoints among the seven member countries regarding the effectiveness (i.e., achieving the intended outcomes) and efficiency (i.e., achieving the intended outcomes in timely manner with the resources available) of the East African Community Medicine Regulatory Harmonisation (EAC-MRH) Joint Assessment Procedure recommended the conduct of a similar study among pharmaceutical company applicants. The aim of this study then was to evaluate the effectiveness and efficiency of the current EAC-MRH operating model from the applicants' perspective, including the challenges and opportunities for improvement.

Methods: Using the Process Effectiveness and Efficiency Rating for Industry questionnaire developed by the authors, data were collected from company representatives responsible for EAC joint procedure submissions.

Results: Responses from 14 study participants underlined the support of pharmaceutical companies for the EAC-MRH initiative, which has facilitated the harmonisation of registration requirements across the EAC region leading to

Abbreviations: ABREMA, Burundi Food and Medicines Regulatory Authority, Republic of Burundi; AMA, African Medicines Agency; AU, African Union; CTD, Common Technical Document; DFCA, Drug and Food Control Authority, Republic of South Sudan; EAC, East African Community; Rwanda FDA, Rwanda Food and Drugs Authority, Republic of Rwanda; GMP, Good Manufacturing Practice; ICH, International Conference on Harmonisation; MRH, Medicines Regulatory Harmonization; NDA, National Drug Authority, Uganda; NMRAs, National Medical Regulatory Authorities; PPB, Pharmacy and Poisons Board, Republic of Kenya; RECs, regional economic communities; SAHPRA, South African Health Products Regulatory Authority; TMDA, Tanzania Medicines and Medical Devices Authority; TWG MER, Technical Working Group on Medicines Evaluation and Registration; WHO, World Health Organization; ZFDA, Zanzibar Food and Drug Medicines and Medical Devices Authority, the United Republic of Tanzania.

one registration for all countries and a reduction of the workload for both applicants and assessors. In addition, it is expected that shorter timelines for approval will lead to improved access to quality-assured essential medicines in the region. Access to various markets at the same time was also noted as an important benefit to pharmaceutical companies. Noted challenges include a lack of process information, a lack of centralised submission and tracking process and a lack of mandated central registration. A key strategy proposed by participants is the establishment of a regional administrative body to centrally receive and track EAC applications and the eventual establishment of a Regional EAC Medicines Authority.

Conclusion: This is the first study evaluating the performance of the EAC work-sharing initiative from the point of view of the applicants. In general, the applicants believe that the system performs efficiently and fulfils its promise. However, some participants indicated that in some countries an EAC positive recommendation does not directly result in an individual country approvals. Following the recommendations listed in this report may mitigate identified areas for improvement and facilitate the overall goal of the EAC-MRH initiative to expedite the availability of needed quality-assured medicines to patients in the region.

KEYWORDS

EAC joint assessment procedure EAC-MRH, effectiveness, efficiency, applicants, common technical documents, joint assessment procedure, pharmaceutical companies

1 Introduction

Countries need fully functional regulatory systems in order to respond to public health needs as well as to enhance access to safe and effective medicines (Kusinitz M et al., 2017). One of the determinants of access to essential medicines is regulatory filing and registration (Sillo et al., 2020). In Africa, regulatory authorities face several challenges in regulating medicines, as most national medicines regulatory authorities (NMRAs) are not adequately resourced when compared with established regulatory authorities. As of 2022, only five NMRAs in Africa, Ghana, Tanzania, South Africa, Egypt and Nigeria have attained the World Health Organization (WHO) maturity level 3 status; that is, a stable, well-functioning regulatory authority (Broojerdi, 2020). Since 2009, the African Union Development Agency (AUDA-NEPAD) has been spearheading the African Medicines Regulatory Harmonisation (AMRH) initiative as a means of improving access to safe, high-quality and effective medicines in Africa through the harmonisation of regulatory requirements (Dansie et al., 2019). Including the East African Community Medicines Regulatory Harmonisation (EAC-MRH) programme, five regional harmonisation initiatives have been established in Africa to increase the number of quality-assured products available to patients, by simplifying the registration processes for manufacturers and improving capacity (Sillo et al., 2020; Ndomondo-Sigonda et al., 2021).

1.1 The EAC-MRH initiative

The EAC-MRH initiative is a joint assessment procedure composed of seven NMRAs in the EAC region. These NNMRAs include Burundi Food and Medicines Regulatory Authority (ABREMA), Bujumbura, Burundi; Kenya Pharmacy and Poisons Board (KPPB), Nairobi, Kenya; National Drug Authority (NDA), Kampala, Uganda; Zanzibar Medicines and Medical Devices Agency (ZMDA), Zanzibar, Tanzania; Drug and Food Control Authority (DFCA), Juba, South Sudan; Rwanda Food and Drugs Authority (RFDA), Kigali, Rwanda; and Tanzania Medicines and Medical Devices Authority (TMDA), Dar Es Salaam, Tanzania.

To provide guidance to the NMRAs in managing applications for registration of human medicinal products in the EAC, a compendium was developed in 2014 by the Technical Working Group (TWG) on Medicines Evaluation and Registration (MER) of the EAC-MRH Project. The compendium has five modules and sets out procedures and requirements for the implementation of Pharmaceutical Products Registration through established Common Technical Documents (CTD) within EAC NMRAs. These documents are based on the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical Products for Human use (ICH) guidelines. The aim of the CTD guidelines is "to provide harmonised medicines registration procedures using the CTD in order to improve access to essential medicines for prevention and treatment of priority disease conditions in the East African region" (EAC Secretariat,

2014). According to Sithole et al. (2022), the CTD format has helped to improve work sharing and the harmonisation of registration requirements and joint reviews in Africa.

With the launch of the EAC-MRH programme in March 2012, member countries have made substantial progress in the reduction of timelines for registration of new medicines using the joint review process. The aim of the regional harmonisation project is to minimise barriers to medicine registration and eventually increase the number of products registered within a shorter timeline. Mashingia and others (2020) reported that from 2012 to 2017 registration timelines were reduced from 24 months to 8–12 months for products reviewed using the new joint assessment process. Started in 2015, the EAC initiative has a decentralised structure, with focus on work sharing and reliance. It is composed of a joint assessment of dossiers for medical products submitted by applicants for review and a joint inspection of manufacturing sites by the assessors (Sillo et al., 2020). As outlined by Ngum and associated (2022), this process has nine steps, starting with the submission of an application and ending with approval at a national level, which is expected to occur within 90 days after a positive recommendation is made. As of December 2021, a total of 159 applications have been received, 144 assessed and 79 products recommended for registration through the EAC-MRH joint procedure, with a median time for recommendation to market authorisation between 30 and 90 days (AUDA-NEPAD, 2021).

A study was conducted in 2021 to determine the views of regulators from the seven NMRAs of the EAC-MRH initiative on the effectiveness and efficiency of the work-sharing initiative. One of the recommendations from this study was to conduct a similar study with the applicants, so that there could be a comparison of the benefits and challenges from the point of view of both key stakeholders (Ngum et al., 2022). The aim of this study was, therefore, to evaluate the effectiveness and efficiency of the current operating model of the EAC-MRH initiative from the applicants' perspective, including the challenges it faces as well as to identify opportunities for improvement.

2 Study objectives

The study objectives were to.

- Obtain the views of the applicants of the EAC-MRH initiative about the performance of the programme to date
- Identify the challenges experienced by applicants throughout the life cycle of the EAC-MRH initiative
- Determine the strengths and weaknesses of the initiative
- Identify the ways of improving the performance of the work-sharing programme
- Envisage the strategy for moving forward.

3 Methodology

3.1 Study participants

From the 34 applicants identified as using the EAC-MRH initiative to submit applications for registration and marketing authorisation, 25 were determined to be eligible for the study; among this group there were 11 non-responses, leading to a 56% response rate. Study participants were distributed into three categories; Generics (foreign); that is, applicants who manufacture generic medicines outside of the EAC region, Generics (local); that is, applicants who manufacture generic medicines within the EAC region, and Innovators; that is, applicants who submitted applications for registration of innovator medicines. During the period of study (2015–2021), there were no local innovators that submitted applications for innovator medicines for registration.

3.2 Data collection

Collection of data started in November 2021 and ended in April 2022. The questionnaire was completed by a representative responsible for EAC joint procedure submissions in each company.

3.3 Development of the PEER-IND questionnaire

The authors developed a Process Effectiveness and Efficiency Rating for Industry (PEER-IND) questionnaire to identify the views of applicants on the benefits, challenges and suggestions for improving the performance of the EAC-MRH work-sharing initiative. (Supplementary) PEER-IND comprised five parts; Demographics; Benefits of the EAC-MRH initiative; Challenges of the EAC-MRH initiative; Improving the performance (effectiveness and efficiency) of the work-sharing programme and envisaging the strategy for moving forward.

3.4 Ethics committee approval

The study was approved by the Health, Science, Engineering and Technology ECDA, University of Hertfordshire, United Kingdom [Reference Protocol number: LMS/PGR/UH/04988].

4 Results

For the purpose of clarity, the results are presented in five parts: Demographics; Benefits of the EAC-MRH initiative; Challenges of the EAC-MRH initiative; Improving the

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TABLE 1 Pharmaceutical companies participating in study.

Name of company	Generics (foreign)	Generics (local)	Innovator
Intas pharmaceutical limited	✓		
Bayer			✓
Cipla Quality Chemical Industries Limited	✓		
Dafra Pharma GmbH	✓		
Impact RH360	✓		
Laboratoire Aguettant	✓		
Laboratory and Allied Ltd.		✓	
Prodigy Healthcare Limited		✓	
Universal Corporation Limited		✓	
La Renon Healthcare Pvt. Ltd. 9 (India)	✓		
Novartis South Africa			✓
F. Hoffmann-La Roche Ltd			✓
Cipla Ltd.	✓		
Amring Farma SRL, Romania	✓		

performance (effectiveness and efficiency) of the work-sharing programme; and Envisaging the strategy for moving forward.

4.1 Part I- demographics

Most respondents, who presented the views of their companies, held roles as head of regulatory affairs in their respective companies, with regulatory experience ranging between 5 and 21 years. The companies that participated in the study were classified according to their product portfolio and location of their manufacturing sites. Eight (58%) were foreign generic pharmaceutical companies, three (21%) were local manufacturers of generics and three (21%) were innovator pharmaceutical companies (Table 1). Of the 144 dossiers/applications assessed as of 31 December 2021, 55% were generics submitted by foreign companies, 22% were new active substances submitted by innovator companies and 23% were generics submitted by the local company.

4.2 The EAC countries in which companies market their products

All the companies indicated they had a separate record of applications submitted for assessment under EAC-MRH to facilitate tracking and adherence to deadlines. The majority of the companies market products in Kenya, Tanzania Mainland and Uganda (Figure 1). The applicants gave various reasons why their companies market products in the selected countries, including the fact that these countries provide excellent and ready market potential for pharmaceutical companies, as wider market coverage maximises revenues and economies of scale. In addition, there is an available patient pool for products in these markets, with market stability and predictability, with an established distribution chain, as well as mature healthcare systems.

Most companies are interested in registering medicines in countries with developed medical systems like oncology and rheumatology centres. The majority of pharmaceutical companies want to ensure maximum reach and access of essential healthcare products to positively impact society and sometimes the marketing of products in these countries is based on partner and donor interest. Companies that are leading manufacturers of essential medicines for high disease burden like antiretrovirals and anti-malarials in the region are marketing medicines and healthcare solutions not only in the EAC member countries, but in the whole of Sub-Saharan Africa.

The capacity of NMRAs in the region is key, as some of the countries have not initiated the process of medicine registration as they do not have fully functional regulatory authorities. Some countries access some medical products through import permits so that marketing in such countries is not required. Aspects such as lack of security, political, and market stability, weak regulatory and healthcare systems, weaknesses in the supply and distribution processes are some reasons why some manufacturing companies do not market products in all EAC countries.

4.3 Part II- benefits of the EAC-MRH initiative to regulators and pharmaceutical companies

Pharmaceutical companies identified the harmonisation of registration requirements across the region, shorter timelines for

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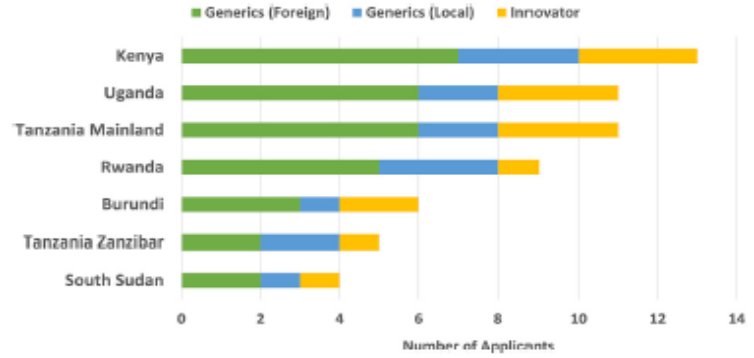

FIGURE 1
EAC countries in which companies market products.

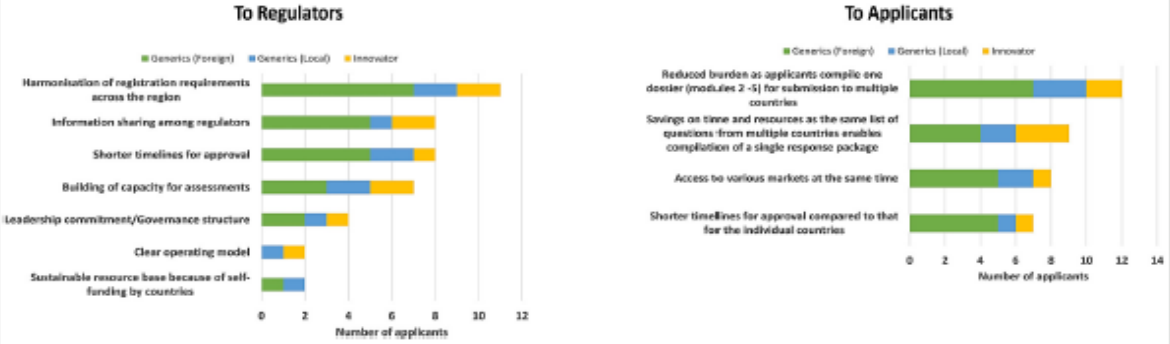

FIGURE 2
Benefits of the EAC-MRH initiative.

approval and information sharing among regulators as well as building capacity for assessments as the top four benefits of the EAC initiative (Figure 2). One registration for all countries was also mentioned as a benefit, leading to access to various markets at the same time. However, it was noted that the shorter approval timelines and clear operating model are currently applicable only for Tanzania.

Several benefits of the initiative were indicated, including reduced burden, as applicants compile one dossier (modules 2–5) for submission to multiple countries, savings in time and resources as applicants receive the same list of questions from multiple countries, which enables the compilation of a single response package. Shorter timelines for approval compared with those for individual countries as well the ability to launch products simultaneously in all markets were also identified (Figure 2).

However, some companies mentioned that they submitted documentation for EAC in August 2019 but did not receive any response from the EAC-MRH Secretariat. Meanwhile, they obtained a national registration for their products based on normal assessment procedure in three countries (Tanzania, Uganda and Kenya). As previously mentioned, others indicated that some of the above benefits are currently applicable only for Tanzania, as the procedure's benefits declined over time for other countries since an EAC positive opinion does not directly result in approval in those countries. Also, NMRAs often request additional information after an EAC positive opinion, which further delays approval and patients' access in individual markets.

The applicants are required to apply for a marketing authorization in EAC countries after a joint positive recommendation. However, the time to registration of the

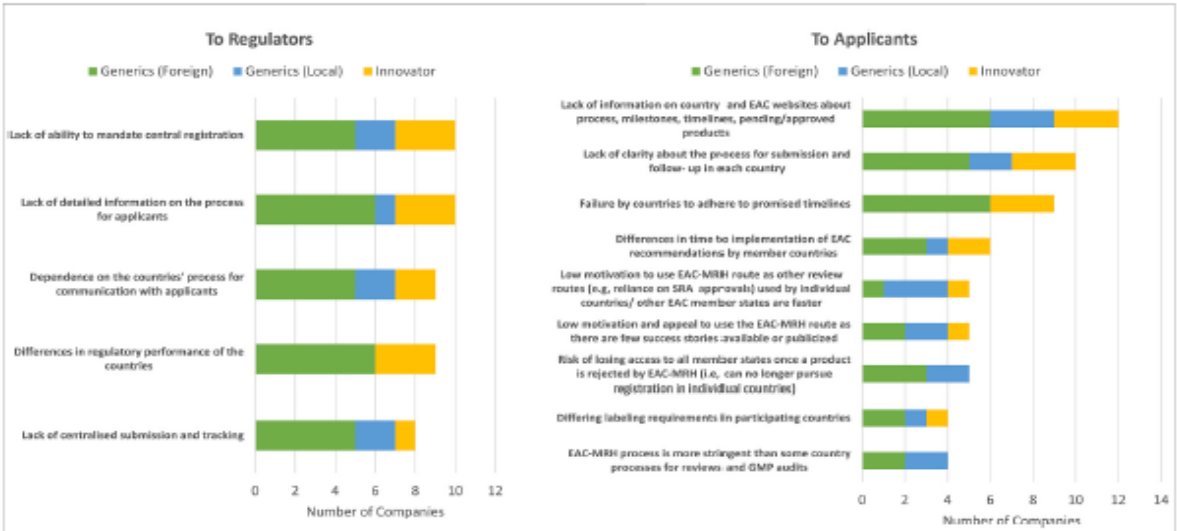

FIGURE 3
Challenges of the EAC-MRH initiative.

product at a country level will depend on when the country specific application is submitted and if additional information is requested by the country. Therefore, the times given for approval represent the time to national approval and not to the time of EAC recommendation. In general, full applications are submitted with only a few abridged dossiers. Most of these applications are for generic products where only quality assessments are conducted. Furthermore, the assessment reports are only from the EAC region. Unfortunately, according to some applicants, their interaction with the EAC procedure has not led to any improvement in product dossier assessment, although their hope is that in the future dossier submission will improve.

Quicker access to quality-assured medicines and increased availability of medicines were the benefits for patients indicated by all applicants, although reduced prices of medicines is not yet an outcome of the initiative for patients.

4.4 Part III- challenges of the EAC-MRH initiative

Some of the challenges of the EAC-MRH initiative highlighted were a lack of detailed information on the process for applicants, differences in regulatory performance of the countries, a dependence on the countries' process for communication with applicants; a lack of centralised submission and tracking processes; an inability to mandate central registration; and an unclear process for obtaining actual marketing authorisation after assessment (Figure 3). Other challenges include the lack of harmonisation between the different EAC member states or harmonisation for variation processes. There is a lack of uniformed and binding requirements for all countries as, although regional guidelines exist, they are not always fully implemented in the national procedures. Also, the presence of country-specific requirements that follow an EAC-MRH positive opinion further delays the approval process.

4.4.1 Challenges faced by applicants making a submission to the EAC-MRH initiative

The top three challenges faced by applicants in making a submission to the EAC-MRH initiative were the lack of information on individual country or EAC websites about the submission process, milestones or timelines or a listing of pending and approved products (Figure 3). Further challenges include a lack of clarity about the process for submission and follow-up in each country, and the failure by countries to adhere to promised timelines.

Other challenges faced by pharmaceutical companies were the differences in time to the implementation of EAC recommendations by member countries; the risk of losing access to all member countries once a product is rejected by EAC-MRH as applicants can no longer pursue registration in individual countries and the need to update online submission and tracking by the applicant.

4.4.2 Challenges faced by authorities in reviewing the EAC-MRH applications

Pharmaceutical companies stated several challenges faced by NMRAs in reviewing the EAC-MRH applications. It was claimed that the EAC-MRH requirements are more numerous and stringent as compared with those of individual countries, so companies need to provide all query details received from EAC. There are different levels of buy-in from individual countries and differing application requirements in some countries; for example, labelling requirements and some medicines are accepted in some countries but not others. The lack of legal/regulatory binding requirements in the national regulations is also a critical challenge and whilst some regional guidelines exist, they are not always fully implemented in the national regulations (Figure 3).

Another challenge is the lack of structured mechanisms for the execution of the joint assessment procedures, and limited capacity delays convening assessment meetings and eventually approvals. There are several logistical constraints including the lack of clear mandate between authorities and the EAC-MRH Secretariat, a lack of a permanent joint Secretariat and shared calendar that include NMRA schedules. Furthermore, the dependence on a single individual with sole responsibility for process at each authority is a key challenge. The coordination for good manufacturing process (GMP) inspections, including desk reviews and the sharing of information between countries was also mentioned as a challenge. The pharmaceutical companies commented that the lack of sustainable resources and funds dedicated to EAC-MRH affects the availability of assessors and the prioritisation of EAC-MRH assessment over national activities (Figure 3).

There is also a constraint in the flow of information among the active NMRAs who participate in the evaluation process, leading to a delay in adopting the recommendations from the outcome of the evaluation process by countries.

4.5 Part IV- improving performance (effectiveness and efficiency)

4.5.1 Improving the effectiveness of the EAC initiative

A number of ways to improve the effectiveness of the EAC initiative were mentioned, which include minimising the need for country-specific documents, engagement and interaction with stakeholders, making publicly available any information that might help applicants in managing their submissions such as document templates, lists of questions and answers, timelines and milestones, disclosure of internal standard operating procedures, consistency in application of guidelines and decisions and the use of risk-based approaches such as reliance pathways were identified by the majority of applicants as ways to improve effectiveness (Figure 4).

4.5.2 Improving efficiency of the EAC-MRH initiative

Most applicants indicated that improving efficiency of the initiative would entail compliance with target timelines by measuring and monitoring each milestone in the review process (Figure 5). It would also include a centralised system for submission of applications and communication with applicants, improved central tracking of EAC products as well as specific and clear requirements made easily available to pharmaceutical companies. An appropriate regulatory framework that recognises and gives appropriate recognition and resources to regional procedures in national regulations would also be invaluable.

4.6 Part V–Strategies for improving the current EAC-MRH operating model

The main proposal made by the pharmaceutical companies to improve the EAC operating model is the establishment of a regional administrative body to centrally receive and track EAC applications. This approach would include being responsible for allocating work, apportioning the applicable fees to countries, tracking of applications and communication with applicants. The majority of the pharmaceutical companies were also of the view that the establishment of a Regional Medicines Authority in the EAC, if legally possible, would be the best strategy for improved performance.

Several reasons were given as to the importance, benefits and strengths of a regional authority and these included an established EAC centre with representatives/staff, which would avoid delays in the assessment process since the evaluation committee will be fully fledged instead of evaluators having to convene from various countries and/or regions. This would harmonise the registration process in the EAC partner states, leading to a less expensive and faster registration procedure. A regional authority would also improve access to medicines as it will enhance other interrelated aspects like the movement of goods, customs requirements as well as having just a license for the product may not be sufficiently efficient to assure product access.

Furthermore, a centralised review with legal responsibility to share reviews, documents, and activities between countries and the industry would minimise overlapping requests for inspections and information sharing. Centralising the evaluation process would increase the efficiency and effectiveness and make communication between stakeholders easier and clearer especially if there are dedicated personnel working in the regional medicines' authority. Applicants would know exactly who to call and interact with regarding their submissions as the employees would only be involved with EAC applications and not applications from individual countries. Applicants also indicated that a regional authority would influence the development of an

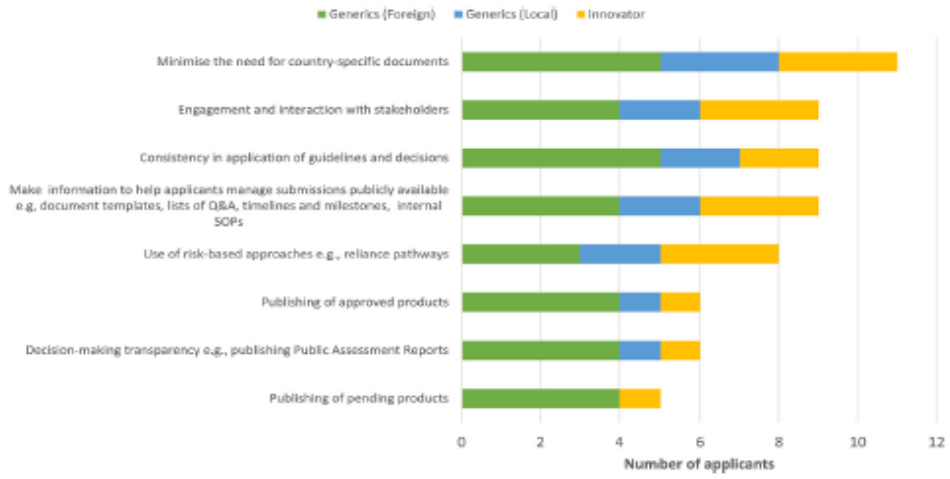

FIGURE 4
Ways to improve the effectiveness of the EAC initiative.

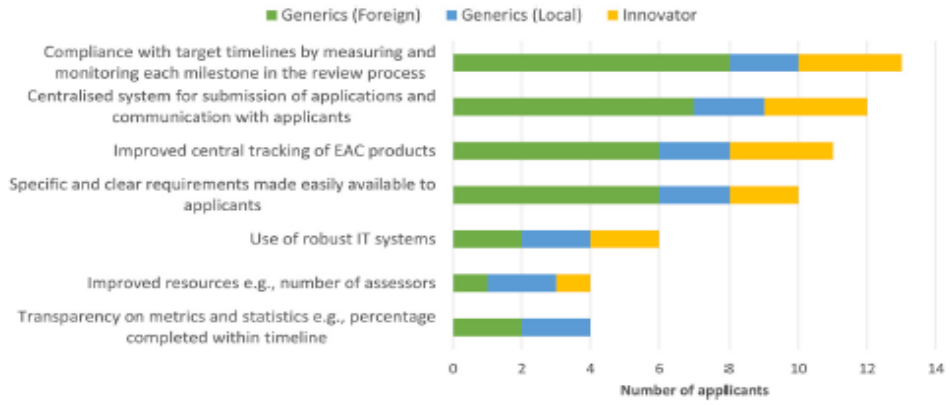

FIGURE 5
Ways to improve the efficiency of the EAC initiative.

online portal for submission and tracking of the application status for the sponsors and also enable a faster and easier approval process with minimum requirements. The ease of verifying information centrally received for EAC-MRH applications would facilitate the tracking of applications and subsequent communication with the pharmaceutical companies.

However, some pharmaceutical companies were of the view that the establishment of a Regional Medicines Authority might not be a good strategy moving forward, especially if it encounters sustainability challenges where the authority has a higher workload and is underfunded. Another proposal was that with the ongoing activities by the African Union toward the operationalisation of the African Medicines Agency (AMA), there is now no additional need for duplication of regulatory processes with protracted lobbying times across the regions. The best approach would be to facilitate ongoing regional

harmonisation frameworks and set the stage for a single Pan-African Agency (AMA). It is important to first clarify the EAC-MRH process, and the role of each individual NMRA, then to fully implement regional procedures in the national authorities. Adding a regional authority without solving the current challenges, would add to the complexity, especially considering that the continental authority (AMA) will soon be fully established. It would also become difficult for applicants to navigate between national, regional and continental institutions, as well as between numerous available registration pathways. Moreover, the challenge of lifecycle management, including post-approval changes submission/approval and license maintenance is still only foreseen by national procedures.

5 Discussion

The aim of this study was to evaluate the effectiveness and efficiency of the current operating model of the EAC-MRH initiative from the applicants' perspective and to identify the challenges it faces as well as opportunities for improvement. Pharmaceutical companies affirmed the importance and relevance of the EAC-MRH work-sharing initiative, as it has benefitted regulators, applicants and patients in the region. As the first region to implement medicines regulatory harmonisation in Africa, the EAC has made major strides toward achieving its main objective of improving patients' access to high-quality medicines in the region. The EAC-MRH initiative has made the process of registration and marketing authorisation more efficient to pharmaceutical companies through the use of harmonised technical standards and optimisation of regulatory requirements, thereby resulting in the reduction of timelines for review of applications (Mashingia et al., 2020; Ndomondo-Sigonda et al., 2020).

Comparing the views of applicants in this study with those of regulators Ngum et al. (2022), identified similar challenges. These included the lack of a centralised submission and tracking process for the work-sharing initiative entailing a lack of clarity about the process for submission and follow-up in each country for applicants. In addition, a lack of ability to mandate central registration has led to a failure by countries to adhere to promised timelines. The regional guidelines that exist are not fully implemented in all the countries. Furthermore, the unclear process for obtaining actual marketing authorisation after assessment through the initiative has caused various levels of company buy-in for the differing application requirements from individual countries. This delay by countries in issuing the actual market authorisation to applicants was affirmed in another study conducted in 2019 by Dansie and associates. The negative effect of the lack of information on individual country and EAC websites cannot be overemphasised and communication from the EAC Secretariat has also been lacking.

Moreover, due to limited capacity and resources, there is a weak coordination mechanism and the lack of structured mechanisms for the execution of the joint assessment procedures. This has led to the dependence of the initiative on the countries' processes for communication with pharmaceutical companies and insufficient engagement between applicants/manufacturers and stakeholders. Finally, as reported by Dansie and others in 2019, the EAC-MRH initiative has not motivated increased company interest in country markets that are less attractive because of political or logistic issues.

5.1 Way forward

As a result of this study, it is recommended that there should be both effective communication and engagement by the industry with the agencies and coordinators should be empowered to talk directly with applicants. There should also be transparency in communication as well as adequate inclusion of all stakeholders, with the industry as a key user of the procedures in the relevant discussions. There should be predictability of processes and adherence to timelines and procedure. There is a need for a holistic approach for the EAC-MRH procedure in terms of eligible product categories and the inclusion of lifecycle management activities. Company study participants also suggested that financial incentives be given to applicants to follow the joint evaluation pathway; that is, fees for joint assessment should be lower when compared with those for single country assessment.

Adherence to the EAC-MRH process by the NMRAs should be promoted. Arik and others also recommended a cooperation framework agreement between NMRAs and the EAC (2020). Instituting a legally binding framework would enhance implementation of joint decisions (Giaquinto et al., 2020) and one of the study participants further suggested the elimination of national assessments of dossiers.

The following are some key recommendations to improve the effectiveness and efficiency of the EAC-MRH initiative.

- A study should be conducted to understand why the benefits of the work-sharing initiative have deteriorated over time in some countries and why a EAC positive opinion does not directly transform to individual country approvals.
- The EAC Secretariat should closely track national marketing authorisations and GMP assessments after a positive joint assessment to ensure that each country implements the registration within an appropriate timeframe.
- Financial incentives should be given to applicants to follow the joint evaluation pathways with the fees per country being lower for joint assessments compared with those for single country assessment.
- There is a need for engagement with the industry with a clear registration procedure for the EAC-MRH process. Clear guidance needs to be implemented based on established harmonised regulations and procedures

across the whole region, and adhered to at the national level.
- Stronger mutual recognition is needed between member countries.
- The establishment of an EAC Regional Medicines Authority would be the best strategy for improved performance.

6 Conclusion

While harmonisation is key to ensuring access to safe, effective and high-quality medicines, there are also other elements of the healthcare system such as accessibility and affordability that need to be in place in order to realise the full benefits of the medicines regulatory harmonisation initiative. It is imperative for the recommendations made in this study to be fully implemented to ensure faster registration of the much-needed essential medicines by patients in the EAC region. Full implementation of the EAC road map 2020–2022 is critical to address some of the immediate issues. It is worth noting that Rwanda, one of the EAC member countries, will be hosting the African Medicines Agency and with the combined efforts by the African Union Partners to strengthen regulatory systems on the continent, the operationalisation of AMA would strengthen the EAC-MRH initiative.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

NN: Designed the study, collected and analysed the data and wrote the first draft of the manuscript. JM and MN-S: Interpreted the results and reviewed the manuscript. SS and SW: Designed the study, interpreted the results, and reviewed the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Evaluation of the Review Models and Approval Timelines of Agencies participating in the East African Medicine Regulatory Harmonisation Initiative: Alignment and Strategies for moving Forward

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Running title: Review Models and Approval Timelines of NRAs in the EAC.

ABSTRACT

Introduction: Over several years, the process of medicines regulatory harmonisation has been embraced by many National Regulatory Authorities (NRAs) to improve public health through faster availability of safe, quality, and effective medical products to patients. This has enhanced harmonisation of technical guidelines and work sharing leading to reduced cost to pharmaceutical companies as they prepare one single set of applications to submit to several countries. After ten years of implementing regulatory harmonisation by the EAC-NRAs, it is now very imperative for these NRAs to rely on each other so as to minimise duplication of use of their limited resources. One of the major challenges in implementing reliance is the lack of clear registration processes in the NRAs and the delay in the approval of medical products. The aim of this study was therefore to compare the review models, target timelines and data

requirements utilised in assessing applications for registration by countries participating in the EAC-MRH initiative so as to align and propose strategies for improvement.

Methods: A validated questionnaire (Optimising Efficiencies in Regulatory Authorities: OpERA) which standardises and captures review processes was completed by the Head of the medicine's registration division in each of the seven EAC-MRH NRAs. A country report based on the completed questionnaire was developed for each NRA. These reports were then validated by the heads of the respective agencies.

Results: Most applications received by all countries were for generics except for Kenya that received a significant number of NAS applications (55 and 53 applications) in 2020 and 2021 respectively. Mean approval times for generics using full review varied with Tanzania's time declining for the three years 202 calendar days in 2020, 93 days in 2022 and 61 days in 2022. Target timelines for full review for the five countries ranged between 180 calendar days (Tanzania) to the highest 330 days (Zanzibar). The three countries (Kenya, Rwanda and Uganda) utilising the verification review model had a target timeline of 90 days while all six agencies conducted abridged reviews. The six NRAs also conducted fast-track assessments through a priority review track. The common technical document (CTD) format was mandatory for applications in all agencies. The targets for key Milestones in the Review Process varied for each country with a few similarities.

Conclusion: The study has provided a baseline for review models, target timelines and data requirements utilised in assessing applications for registration by countries participating in the EAC-MRH initiative. Implementing the recommendations from this study will enable the NRAs to align and improve their registration processes.

Key Words: EAC Joint Assessment Procedure; Review Models; Approval Timelines; Regulatory Reliance

INTRODUCTION

One of the key functions of National Medicines Regulatory Authorities (NRAs) is the review of applications and registration of medical products submitted by pharmaceutical manufacturing companies. The NRAs are expected to have effective and efficient regulatory systems to ensure that the timely marketing authorisation is granted to safe, effective and good quality medical products. One of the objectives of establishing the EAC-MRH project was to build capacity of NRAs in the region through work sharing, training and twinning. Currently there is a strong advocacy on reliance especially as most of these agencies delay issuing marketing authorisation for medical products leading to a significant backlog.

Over several years, the process of medicines regulatory harmonisation has been embraced by many National Regulatory Authorities (NRAs) to improve public health through faster availability of safe, quality, and effective medical products to patients. This has enhanced the harmonisation of technical guidelines and work sharing leading to reduced costs to pharmaceutical companies as they prepare one single set of applications to submit to several countries. After ten years of implementing regulatory harmonisation by the EAC-NRAs, it is now imperative for these NRAs to rely on each other so as to minimise duplication of their use

of limited resources. One of the major challenges in implementing reliance is the lack of clear registration processes in the NRAs and the delay in the approval of medical products.

Reliance

With the complexities that come with the granting of marketing authorisation for medical products, most regulatory authorities are now embracing the concept of reliance as a way of improving performance. It is now clear that no one agency can do it all especially with new advanced health technologies and emerging public health diseases plaquing the world. The main objectives of the harmonisation initiative are to build trust amongst NRAs so that they can rely on each other's decisions. According to the World Health Organisation (WHO) guidelines on good reliance practices, NRAs are encouraged to implement reliance to minimise duplication of effort especially given their limited resources. Countries with weak regulatory systems are called upon to rely on the WHO Listed Authorities (WLA). According to the CIRS 2022 R&D briefing 85, there has been an increase in the use of facilitated regulatory pathways even by well-resourced NRAs in the past five years for approval of new medicines to ensure patients' timely access to safe, quality and effective medical products. Therefore, Regulatory reliance and work sharing will help low- and middle-income countries to have access to innovative medicines in a timely manner (McAuslane et al, 2023).

Registering Medical Products in LMICs:

The main function of NRAs is to register medical products in their countries. This is also known as granting marketing authorisation or product licensing (Rago et al, 2008). Countries have different regulatory requirements for the registration of pharmaceutical products. Understanding the review models and approval timelines for the East African Community as an emerging market for pharmaceutical companies is critical (Shelke et al,2020) in fast tracking the registration process to provide the much-needed medical products to patients in a timely manner. There has been a general indication that for applicants interested in these markets that the NRAs should ensure that the application procedures are clear, that communication and transparency is enhanced, with timelines for approval of products clearly outlined, with registration guidelines for countries in the same region being harmonised and registration processes being effective and efficient (Sithole et al, 2021; Ngum et al, 2022). However, reviewers have also raised the challenge that the long review timelines experienced in the registration of medical products are sometimes caused by the delay in manufacturers' or applicants' response to queries. It is therefore important to understand that these requirements from the regulatory authorities on the review models used should inform the industry and other stakeholders on what to expect from the agencies. The first paper of this series focused on comparing the key milestones in the review process using a general model with a process map and milestones. It also examined how these agencies build quality into the review by analysing their good review practices. Lastly this paper has examined how quality is built into the decision-making practices of the EAC NRAs as it reviews whether there are measures in place to guide good decisions.

The aim of this paper which is the second of this series is to compare the review models, target timelines and data requirements utilised in assessing applications for registration by countries participating in the EAC-MRH initiative so as to align and propose strategies for improvement.

METHODS

Study participants

The study participants included Senior Programme Officers from the Medicines registration divisions in the seven NRAs; Pharmacy and Poisons Board-PPB, Kenya; National Drug Authority-NDA, Uganda; The Tanzania Medical Devices Authority (TMDA); Zanzibar Food and Drugs Authority (ZFDA) Tanzania; Drug and Food Control Authority DFCA South Sudan; Burundi Food and Medicines Regulatory Authority (ABREMA) and Rwanda Food and Drugs Authority.

Data Collection

A validated questionnaire (Optimising Efficiencies in Regulatory Authorities: OpERA) describing the organisation structures, regulatory review systems for market authorisation of new active substances (NASs) and generics including their overall timelines from the date of submission of the application to when it is approved, good review practices (GrevP) and quality decision making practices, was completed by each of the agencies in 2022 and 2023. The questionnaire is composed of six different parts: Part 1 documents the organisation of the agency with the focus on its structure and resources; Part 2 covers the types of review models used by the agency for the scientific assessment of medicines; Part 3, is based on key milestones in the review process with the focus on the process map and milestones; Part 4 relates to good review practices (GrevP) and how an agency builds quality into their regulatory processes; Part 5 focuses on the quality of the decision-making processes based on whether the agency have good measures in place to guide decision making, and Part 6 describes the challenges and opportunities available to the national regulatory agencies (Appendix 3).

Models of Regulatory Review

A Risk based approach to the review involves different review models which describe the ways in which agencies access the scientific data received from applicants during the assessment process. This can vary depending on whether the data is assessed in detail by the agency, or the agency relies on results of the assessment conducted elsewhere. The decision to choose which type of review model will also depend on the type of product and its status with other agencies.

The different steps in the review process do have a significant effect on the review timelines and subsequent market authorisation. There are three types of review models which NRAs can use namely;

The verification review (Type 1): which is used to minimise duplication by allowing a product that has been registered in a recognised agency to be marketed in the receiving country. The main responsibility of the receiving country is to verify that the product has indeed been registered elsewhere and is exactly the same product.

The abridged review (type 2) model also minimises the use of resources by not reviewing scientific data that has been assessed elsewhere but focuses on reviewing the product based on its local conditions which could be climate, infrastructure for distribution, benefit-risk assessment, and medical practice culture.

The full review (type 3) is when the agency assesses the complete application including all the scientific data. This is carried out with applications that have not been reviewed elsewhere and requires more human resources and an improved infrastructure.

RESULTS

For the purpose of clarity, the results of this study will be presented in three parts: Part 1: Metrics of applications received and registered; Part 2: Review models, extent of scientific assessment and data requirements and Part 3: targets of key milestones in the review process.

Part 1: Metrics on NASs, generics, and WHO Prequalified Generics

All seven countries completed the OpERA Questionnaire. However, South Sudan did not report any data since they had not received any application for the specified study period. Kenya received 55 applications for NASs in 2020 and approved 18 and received 53 applications in 2021 out of which 47 were approved. In 2022 Rwanda received 409 applications for NAS and approved 160 and in 2023 received 398 applications and approved 60. (Table 4.1).

All the six NRAs received applications for generics with Tanzania approving the highest number of applications (499) for 2020 and (503) for 2021. It is interesting to note that the number of generics approved by Tanzania dropped in 2022 to 359. Kenya had received more applications (692) in the same year (2020), but only granted marketing authorisation for 81 products. Burundi in 2020 received 157 applications and approved 110 but in 2023 approved 57 with 342 applications received. In 2021, Kenya received 909 applications and only approved 368 while Uganda received 849 and approved 405. Burundi on the other hand did not approve any product in 2021 even though they received 68 applications. Uganda received the highest number (849) of applications in the region in 2021 and was able to register 405 generic products during the year. Tanzania in 2021 received 704 applications and registered 503 while Zanzibar received 10 applications in the same year but only approved two in 2022 (Figure 4.1).

Kenya and Rwanda saw a slight increase in WHO pre-qualified generics approved in 2021 while Burundi and Zanzibar did not receive WHO pre-qualified applications. Tanzania in 2021 received 15 WHO pre-qualified applications and approved 13. For Uganda there has been a decline in the number of WHO pre-qualified applications from 2021 to 2023 (Table 4.1).

Mean Approval Times

While Kenya received a number of applications for NASs, they approved 18 applications in 2020 and 47 applications in 2021 (Table 1), but they did not indicate the mean approval times for a full review of NAS applications (Table 4.2). For full review of generics, Tanzania saw a decline on the mean approval times for the three years consecutively (202 days in 2020, 93

days in 2021 and 61 days in 2022) to approve generics. Rwanda took (1035 days) in 2022 and declined to 735 days in 2023 while Kenya increased from 575 days in 2020 to 739 days in 2021 days by Kenya in 2021. Zanzibar also increased from 480 days in 2021 to 630days in 2022. The mean approval timelines for generics Uganda saw a slight decrease in 2022 (283 days) from 261 days in 2021. However, there was an increase in 2023 to 238 days. (Figure 4.2).

For WHO pre-qualified applications, Rwanda (484 days) and Kenya (341days) took a longer mean approval times using full review while the other countries took less than 100 days for the approval of generics (Table 4.2).

Using verification review type, an average of 90 days was used by Burundi and Zanzibar in 2022 for WHO pre-qualification. Zanzibar also reported taking a mean approval time of 78 days to review the EAC-MRH recommended applications. From 2020 to 2023, Uganda has less that 65 days as mean approval times for generics and WHO pre-qualified products. Kenya and Rwanda did not report the mean approval times for verification review type for NASs, Generics and WHO pre-qualified applications (Table 4.2).

For the abridged review type, Zanzibar spent 180 days in 2020 as mean approval times for generics. Burundi took 90days in 2022 for WHO pre-qualification while Tanzania took 14 days in 2021 and 13 days in 2022. In 2021, Rwanda took 484 days for approval of WHO pre-qualification application. Kenya and Rwanda did not submit information on mean approval times when using the abridged review type (Table 4.2).

Part II: Review Models Used for Scientific Assessment

All of the six agencies carry out full and abridged reviews for scientific assessment.

Verification Review (Type 1)

Burundi, Tanzania and Zanzibar do not conduct verification reviews for generics. However, Burundi and Zanzibar do use verification review for WHO prequalification and EAC-MRH recommended applications. The reason for not implementing type 1 assessment by TMDA is that they do not implement mutual recognition policies yet. The agency offers special import permits based on its regulations. Kenya and Rwanda conduct verification reviews for selected applications like WHO pre-qualified products, and products approved by WHO Listed Authorities (WLA) and agencies who have valid agreements to share reports. For Uganda, this is for WHO collaborative registration procedure (CRP) and EAC-recommended products (Table 4.3).

Reference agencies used by the NRAs include WHO-prequalification programme agencies, ICH founding members and WLAs such as Swissmedic, mature European Union agencies, European Medicine Agency (EMA), United States Food and Drug Authority (US FDA), Health Canada, Medicines and HealthCare Products Regulatory Authority (MHRA), Japan's Pharmaceuticals and Medical Devices Agency (PMDA), Global Health Products (MAGHP) Australia's Therapeutic Goods Administration (TGA). In addition to WLAs listed above, East African Community work sharing Initiative (EAC-MRH), Intergovernmental Authority on

Development (IGAD), TMDA and Ghana FDA were also reference agencies for PPB. All three countries had a 90 days target time for the verification review.

Abridged Review (Type 2)

All six agencies conducted abridged reviews. Type 2 assessment is used by Burundi-ABREMA for selected applications such as products that have been registered by WHO, WLAs, PPB, NDA, TMDA and EAC recommended products. While Kenya, Rwanda, Tanzania and Zanzibar use abridged reviews for selected applications that were previously approved by WHO-prequalified and WLA-approved products. For Tanzania, these selected applications must be approved in at least two reference countries, and not rejected in any other reference country. Uganda utilises the abridged review pathway for Over the Counter (OTC) products. Products category reviewed by Zanzibar are NAS, major line extensions, generics and biosimilars. Kenya and Uganda had a target time of 105 calendar days, Rwanda 90 calendar days, and Tanzania 126 days (Table 4.3).

Full Review (Type 3)

All six agencies conduct type 3 assessment for all applications that do not qualify for type 1 or type 2 data assessments. Only Kenya and Tanzania conduct Type 3B (a full, independent review of pre-clinical (safety) and clinical (efficacy) is carried out) for all major applications. The other agencies conduct type 3A where data on quality, pre-clinical (safety) and clinical (efficacy) are assessed in detail but there are requirements for pre-registration elsewhere before the authorisation can be finalised (Table 4.3).

Only Burundi did not have a target time for full review of applications, but Tanzania had the lowest of 252 calendar days, followed by Uganda with 261 days, then Kenya 262 days, Rwanda 270 days, and Zanzibar with 365 days (Table 4.3). Table 6 further provides data for these targets with respect to major milestones.

Fast-Track/Priority Review

All six agencies conduct fast-track assessments through a priority review systems. Only Tanzania and Zanzibar indicated a target timeline of 90 and 126 calendar days respectively for review of fast-tracked applications in 2022 (Table 4.3). The agencies conduct a rapid assessment of the application to obtain pharmacological, marketing/commercialization, pharmacovigilance, and clinical trials additional information. Applicants were charged a higher fee for priority review that achieve a shorter timeline.

Data Requirements

The Certificate of a Pharmaceutical Product (CPP) is required with the application or before authorization is issued for all six agencies. The common technical document (CTD) format is mandatory for applications in all agencies. For all review types, all agencies required submission of full data for Modules 1-5 and Summary data for modules 2.3, 2.4 and 2.5.

The agencies then conduct a detailed assessment, and an evaluation report is prepared. Other factors considered in assessing risks and benefits were differences in medical culture/practice, ethnic factors, and national disease patterns. The agencies also endeavour to obtain internal

assessment reports from other agencies such as the referenced agencies, use of public assessment reports on the internet such as the European Public Assessment Reports (EPARs) or through their participation in the WHO collaborative registration procedure where access is given for reports of prequalified products. All six agencies also have access to reports assessed through the EAC-MRH Initiative as they all participate in the EAC medicine regulatory harmonisation program. A primary scientific review is conducted by the agency staff although Tanzania include external reviewers.

Apart from Kenya and Zanzibar, the other four agencies set targets for review times spent on the scientific assessments. Only Uganda does not have a recording procedure that allows the company response time to be measured. All the agencies recognise medical urgencies and thus implement priority reviews for qualifying products. Only Tanzania conducts sequential processing of technical data. For all six agencies, physicians are less than 25% of the medical staff within the agencies' review staff. Although all the agencies have an approval times target for the overall time for the review and approval of an application (Table 4.5).

FIGURE 4.1 | Comparison of number of generics approved from 2020 to 2023.

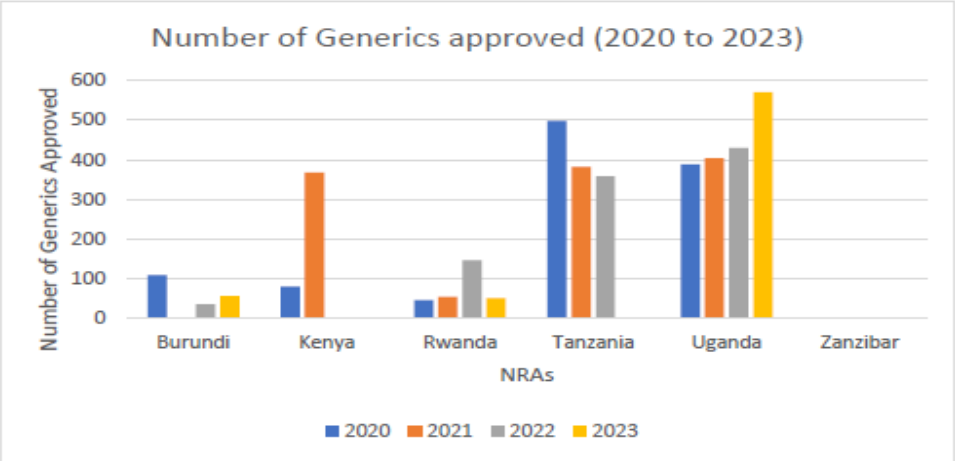


Figure 4.2: Comparison of mean approval times for generics using full review from 2020 to 2023

8

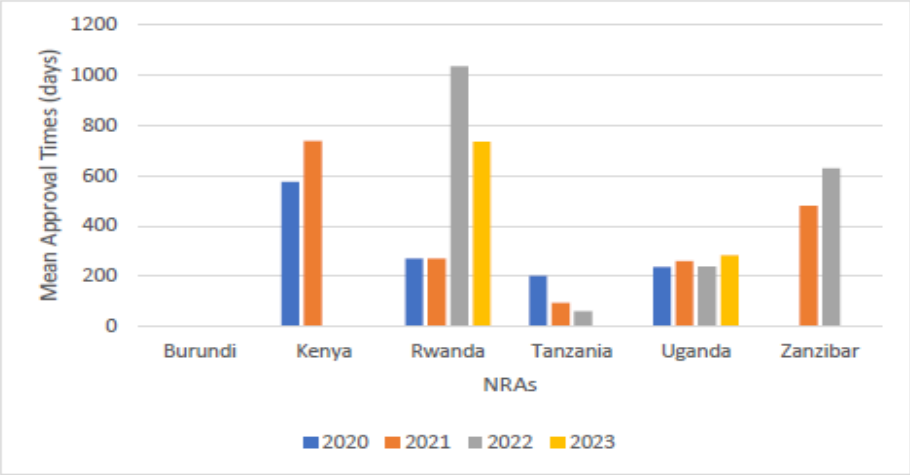

1200
1000
800
600
400
200
0
Mean Approval Times (days)
Burundi
Kenya
Rwanda
Tanzania
Uganda
Zanzibar
NRAs
2020
2021
2022
2023

TABLE 4.1 Comparison of metrics for NASs, generics, and WHO prequalified generics (2020–2023).

Country	Burundi				Kenya				Rwanda				Tanzania				Uganda				Zanzibar			
Year	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023
NASs																								
Received	0	0	0	0	55	53			0	0	409	398	0	0	0	0	NS	NS	0	0	0	0	0	0
Approved	0	0	0	0	18	47			0	0	160	60	0	0	0	0	NS	NS	0	0	0	0	0	0
Generics																								
Received	157	68	80	342	692	909			533	615	390	379	631	975	1,079	764	508	849	804	905	8	10	14	22
Approved	110	0	36	57	81	368			46	55	147	51	499	383	359	51	389	405	430	571	1	2	0	0
WHO Pre-qualification																								
Received	0	2	0	1	10	35			16	18	7	3	7	22	16	14	10	12	7	6	1	0	0	0
Approved	0	0	4	1	10	20			0	11	7	0	7	14	13	12	10	12	7	3	1	0	0	0

NASs, new active substances; WHO, World Health Organization; N/S, Not specif

Table 4.2: Comparison of mean approval times NASs, generics and WHO prequalified generics 2020-2023 (calend1ar days)

N/A Not Applicable

N/A1- Not Available

Country	Burundi				Kenya				Rwanda				Tanzania				Uganda				Zanzibar			
Year	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023
Full review																								
NASs	N/A	N/A	N/A	N/A					N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0	0	N/A	N/A	0	0	0	
Generics	N/A	N/A	N/A	N/A	575	739			270	270	1035	735	202	93	61	85	237	261	238	284	0	480	630	
WHO Pre-qualification	N/A	N/A	90	90	N/A	341			90	90	484	90	83	N/A	N/A	79	54	60	56	65	0	0	0	
Verification																								
NASs	N/A	N/A	N/A	N/A									N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Generics	N/A	N/A	N/A	N/A									N/A	N/A	N/A	N/A	N/A1	N/A1	54	43	0	0	78	0
WHO Pre-qualification	N/A	N/A	90	90									N/A	N/A	N/A	N/A	54	60	56	65	90	90	90	
Abridged																								
NASs	N/A	N/A	N/A	N/A									N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0	0	0	
Generics	N/A	N/A	N/A	N/A									241	153	93	N/A					180	0	0	
WHO Pre-qualification	N/A	N/A	90	90							484	90	N/A	N/A	N/A	N/A					0	0	0	

Table 4.3: Review models employed and target timelines (calendar days - 2022-2023)

Type of review model	Burundi	Kenya	Rwanda	Tanzania	Uganda	Zanzibar
Verifications review (type 1)	x	✓c	✓c	x	✓a	x
Target	N/A	90	90	N/A	90	N/A
Abridged review (type 2)	✓b	✓c	✓c	✓c	✓e	✓c
Target	N/A	105	90	126	105	126
Full review (type 3)	✓3A	✓3B	✓3A	✓3B	✓3A	✓3A
Target	N/A	262	365	180	261	365
Fast Track/Priority Review	✓	✓	✓	✓	✓	✓
Target	N/A	N/A	N/A	90	N/A	126

aFor WHO collaborative registration procedure (CRP) and EAC-recommended products.
bFor WHO CRP, WHO Listed authority (WLA)-approved and EAC-recommended products.
cFor WHO-prequalified and WLA-approved products.
dFor legacy molecules with minimal risk.
eFor OTC products

Table 4.5: Summary comparison of key features of the regulatory systems for medicines.

Marketing authorisations	Burundi	Kenya	Rwanda	Tanzania	Uganda	Zanzibar
Certificate of a Pharmaceutical Product (CPP): CPP is required with the application or before authorization is issued	✓	✓	✓	✓	✓	✓
Common technical document (CTD): CTD format is mandatory for applications	✓		✓	✓		✓
Medical staff: More than 25% within the agency review staff are physicians	x	x	x	x	x	x
Review times: The agency sets targets for the time it spends on the scientific assessment of NASs and generic applications	✓	x	✓	✓	✓	x
Approval times: The agency has a target for the overall time for the review and approval of an application	✓	✓	✓	✓	x	✓
Questions to sponsors are batched at fixed points in the review procedure	✓	✓	✓	✓	✓	✓
Company response time: Recording procedures allow the company response time to be measured and differentiated in the overall processing time	✓	✓	✓	✓	x	✓
Priority reviews: The agency recognizes medical urgency as a criterion for accelerating the review and approval process for qualifying products	✓	✓	✓	✓	✓	✓
Sequential processing: Different sections of technical data reviewed sequentially rather than in parallel	x	x	x	✓	x	x
Price negotiation: Discussion of pricing is separate from the technical review and does not delay the approval of products	x	✓	x	x	✓	✓
Sample analysis: The focus is on checking quality in the marketplace and requirements for analytical work do not delay the marketing authorization	✓	x	x	✓	✓	✓

Table 4.4: Extent of scientific assessment for full review.

	Burundi	Kenya	Rwanda	Tanzania	Uganda	Zanzibar
Chemistry, manufacturing and control (CMC) data extensive assessment				✓		✓
Non-clinical data extensive assessment	✓	✓	✓	✓	✓	✓
Clinical data extensive assessment	✓	✓	✓	✓	✓	✓
Bioequivalence data extensive assessment				✓		
Additional information obtained (where appropriate)	✓	✓	✓	✓	✓	✓
Other agencies internal review reports	✓	✓	✓	✓	✓	✓
Medical and scientific literature	✓			✓		

A For biosimilar products not approved by a reference agency only.

TABLE 4.6 | Comparison of targets for key milestones in the full (type 3) review process -(calendar days).

Target	Burundi	Kenya	Rwanda	Tanzania	Uganda	Zanzibar
Receipt and validation (A – B)	90	3	30	5	No target time	90
Queuing (B – C)	60 -180	<365	60-150	35	365	60-180
Primary scientific Assessment (C – D)	90	No target time	No target time	100	180	180
Questions to applicant (Clock stop) (D – E)	90	180	90	60	180	180
Review by Expert Committee (G – H)	90	No target time	60	1	30	1
Approval procedure (Admin)	30-90	<30	<30	<30	30-90	<30
Overall approval time (A – I)	90	730	365	180 (exc. Applicant time	547	365

Part III: Targets for key Milestones in the Review Process

In line with good review practices, each regulatory agency should set a target timeline for each milestone and the overall process. In the first article of this series, the review process, and key milestones for the six agencies were reported. This article reviews the target timelines for these key milestones. The standardised process map for review and approval of medical products (Figure 4.3) demonstrates key milestones that are usually recorded and monitored by mature regulatory agencies in the review of applications.

Receipt and Validation

Uganda had no target time for receipt and validation of applications. Kenya had lowest of three days, followed by Tanzania with 5 calendar days, then Rwanda with 30 days. Both Burundi and Zanzibar had 90 calendar days as their target (Table 4.6).

Queue Time

This is the time taken to start the scientific assessment after the application has been validated or accepted for review. Uganda and Kenya had the longest queue time of 365 days, followed by Burundi, Rwanda and Zanzibar with queue time ranging from 60 to 180 calendar days. Tanzania had the shortest queueing time of 35 calendar days (Table 4.6).

Primary Scientific Assessment

Tanzania had the shortest target for primary scientific assessment of 60 calendar days followed by Burundi with 90 days which also included peer review. Uganda and Zanzibar has 180days. Kenya and Rwanda did not have target times (Table 4.6)

Questions to Applicants

Here the clock stops as the assessment is paused and time given to the sponsor to respond to any queries. The target was 90 days for Burundi and Rwanda, and 180 days for Kenya, Tanzania, Uganda, and Zanzibar (Table 4.6).

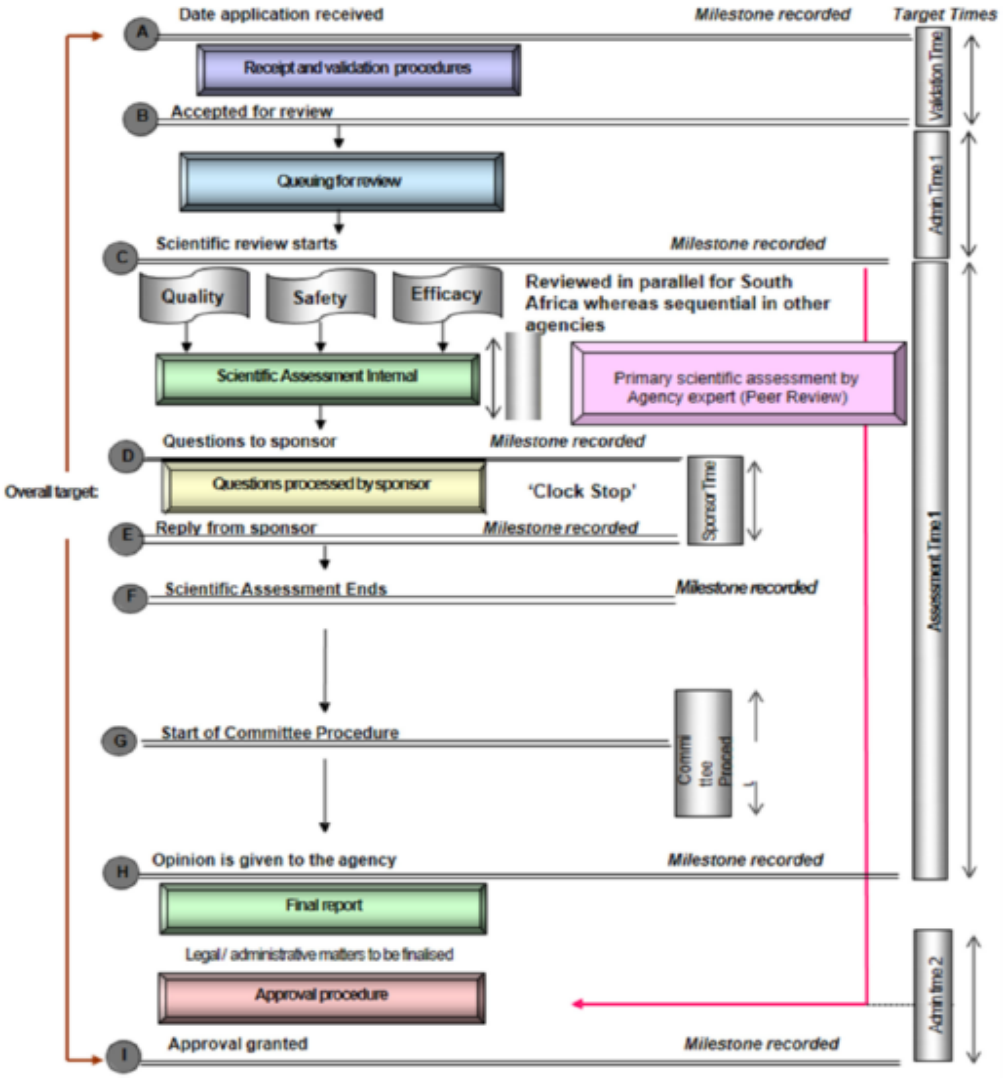
Review by Expert Committee

Four of the agencies use expert committees to make decisions on approval or refusal of marketing authorisation of medical products. Zanzibar does not use expert committees; Tanzania takes one day to make the expert committee decision while Uganda takes 30 days followed by Burundi with 90 days. Kenya and Rwanda do not have target times (Table 4.6).

Authorisation Procedure

This is the time it takes to issue the overall approval after the scientific opinion has been made. Four of the agencies (Kenya, Rwanda, Tanzania, Zanzibar) take less than 30 days. Uganda takes between 30 to 90 days, however, the sponsor is informed of a positive scientific opinion before the authorisation is issued whereas Burundi did not give a target (Table 4.6).

Figure 4.3: Standardised process map for the review and approval of medical products (adopted from Sithole et al, 2021)



DISCUSSION

The aim of this study was to compare the review models, target and review timelines as well as data requirements utilised in assessing applications for registration by countries participating in the EAC-MRH initiative to align and propose strategies for improvement. Countries with higher populations received higher numbers of applications and are also autonomous agencies. Ozawa et al, 2019 in his studies demonstrates how improving the autonomy of health facilities improves access to essential medicines.

It is interesting to note that only one country in the region received applications for New Active substances (NAS) in 2020 and 2021. This is not surprising as several studies have highlighted a similar view that the number of NAS launched in low- and middle-income countries are very few as compared to high-income countries (Gwaza, 2016; Sithole et al, 2021). Most innovative medicines or new medicines are usually first approved by well-resourced regulatory agencies (Rago, 2008). The study by CIRS (2022) reported how six major regulatory authorities (Europe, USA, Japan, Canada, Switzerland and Australia) have used facilitated regulatory pathways and internationalisation for approvals of new medicines. It is hoped that with the operationalisation of the African Medicines Agencies (AMA), many new and complex molecules applications will be submitted through the AMA. It would be important to understand the reason for a decline in the number of applications received and approved by Burundi in 2021 as compared to 2020 and it is also important to note the decrease in mean approval times for generics in Tanzania from 202 days in 2020 to 61 days in 2022.

All the six agencies in the region are implementing reliance as the majority employ the verification and abridged review models. It is important to note that countries in this region are already relying on each other which is the major success of the EAC work sharing initiative. To enhance collaboration, it will be critical for these countries to have mutual recognition or cooperation agreements especially for Tanzania who is unable to implement the verification review due to the absence of mutual recognition agreements. It is also going to be beneficial for inter-REC reliance to be instituted for the REC-MRH Initiatives so that the different regions can also rely on the decisions of each other. This study provided a clear understanding of the review processes and regulatory requirements for registration of medical products in the agencies in East Africa. This will act as a baseline for future studies especially when there will be need to evaluate progress and identify any improvements as the African Medicines Agency (AMA) becomes operationalised. Other agencies have also been given the opportunity to better understand these review processes and can learn from each other as they share experiences.

RECOMMENDATIONS

As a result of this study, the following recommendation should be considered by the six agencies taking part in this study.

1. **EAC-MRH as a reference agency**: All agencies participating in the EAC-MRH initiative should consider formally recognizing EAC-MRH as a reference agency for a reliance pathway.

2. **Timelines and targets:** Agencies should consider documenting the all key milestones and relevant timelines in order to monitor and measure their regulatory performance.

3. **Information system:** NRAs should develop information systems that can track registration timelines from the date the application is received to the date the registration is granted.

4. **Mutual recognition:** Develop and implement mutual recognition agreements to enhance reliance practices amongst NRAs in the region as well as inter-REC reliance.

5. **Communication to applicants:** All agencies should communicate their regulatory requirements to applicants on their website in order to facilitate a seamless review process as well as improving timelines.

6. **Capacity building:** Agencies should consider the following:

- Exchange of staff between agencies
- Secondments
- In-house education and training and continuous professional development

CONCLUSION

This study serves as the first comparative evaluation of the review models for the national medicines' regulatory authorities of the EAC countries. It has provided a baseline for review models, target and review timelines as well as data requirements utilised in assessing applications of medical products for registration by countries participating in the EAC-MRH initiative. It is important for NRAs to have open-minded discussions, document best practices and share experiences so as to learn from each other or from reference agencies. The reliance mechanisms should be developed and implemented by the countries in the region. Implementing the recommendations from this study will enable the NRAs to align and improve their registration processes.

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Original Article

Comparison of Three Regional Medicines Regulatory Harmonisation Initiatives in Africa: Opportunities for Improvement and Alignment

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Abstract

Background: The African Medicines Regulatory Harmonisation (AMRH) Initiative was formed in 2009 and subsequently, three regional initiatives (East African Community Medicines Regulatory Harmonisation [MRH], Southern African Development Community [SADC]/ZaZiBoNa MRH, and the Economic Community of West Africa States MRH) were established. As these initiatives serve as a foundation for the African Medicines Agency (AMA), the aim of this study was to compare their operating models, successes and challenges to identify opportunities for improvement and alignment.

Methods: A mixed method approach was used for the data collection using a questionnaire, the Process, Effectiveness and Efficiency Rating (PEER), developed by the authors specifically for this study and semi-structured interview techniques. There were 23 study participants (one from each agency of the member countries of the three regions). It was hoped that data generated from this study would lead to a series of recommendations, which would then be ratified by the regulatory authorities.

Results: Most respondents stated that AMRH contributed to the strengthening of regulatory systems and harmonising regulatory requirements across economic regions of Africa, potentially resulting in improved access to quality-assured medicines. Although established at different times and at the discretion of each region, the marketing authorisation application review processes are largely similar, with a few differences noted in the eligibility and submission requirements, type of procedures employed, the timelines and fees payable. The challenges identified in the three regions are also similar, with the most noteworthy being the lack of a binding legal framework for regional approvals.

Conclusion: In this study, we compared the process, successes and challenges of these three regional harmonisation initiatives in Africa addressing the areas of legal frameworks, information management systems, the accessibility and affordability of medicines and reliance that will bring greater alignment and efficiency in their operating models, thereby strengtheni the foundation of the soon-to-be-operationalised AMA.

Keywords: Medicines Regulatory Harmonisation, Africa, African Medicines Agency, EAC, ZaZiBoNa, SADC, ECOWAS

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Background

It is the responsibility of national medicines regulatory authorities (NMRAs) to ensure that medical products such as medicines and vaccines used by the public are of good quality, safe and effective.[1] The role of NMRAs was brought into the spotlight during the COVID-19 pandemic, as these agencies were responsible for the review and approval of novel vaccines in the shortest possible time. This public health emergency resulted in an increase in the use of reliance and collaborative registration pathways among regulatory authorities, as they sought to shorten the time to market various life-saving medical products.[2]

Reliance is defined by the World Health Organization (WHO) as "the act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, in reaching its own decision" (Figure 1).[3,4] The foundation for NMRA use of reliance was built prior to the COVID-19 pandemic, when NMRAs invested in implementing reliance principles to improve efficiency and establish the relevant systems in accordance with the WHO good reliance practices guidelines.[3,5] A type of reliance is joint review or work sharing, in which the review or assessment of a medicine is conducted by two or more NMRAs collaboratively. Examples of joint review or work-sharing initiatives are the East African Community Medicines Regulatory Harmonisation (EAC MRH) initiative, the ZaZiBoNa/Southern African Development Community Medicines Regulatory Harmonisation (SADC MRH) initiative and the Economic Community of West African States Medicines Regulatory Harmonisation (ECOWAS MRH) initiative currently implemented in Africa through the African Medicines Regulatory Harmonisation (AMRH) Initiative established in 2009.[6]

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Key Messages

Implications for policy makers

- Information is needed regarding the operating models and successes and challenges experienced to date for the three initiatives for medicines regulation established in the economic communities of Africa under the auspices of the African Medicines Regulatory Harmonisation (AMRH) Initiative.
- Qualitative questionnaire and literature search data reveal that the marketing authorisation application review processes of the three Medicines Regulatory Harmonisation (MRH) programmes, the East African Community; Southern African Development Community/ZaZiBoNa; and Economic Community of West African States are largely similar, with a few differences noted in the eligibility and submission requirements, type of procedures employed (eg, centralised or decentralised), the timelines and fees payable.
- Participants uniformly agreed that harmonisation of regulatory requirements, information sharing and capacity building are the primary benefits of the MRH initiatives, whilst the principal challenges of the programmes are a lack of centralised submission and tracking and inconsistency in stringency of submission requirements.
- Recommendations to mitigate these challenges include the alignment of operating models; development of a regional legally binding framework to allow establishment of a centralised procedure; formation of information management systems and support of capacity strengthening to facilitate mutual recognition and reliance.
- The recommendations made in this study will bring greater alignment and efficiency to the operating models of the three regional harmonisation initiatives, strengthening the foundation of the soon to be operationalised African Medicines Agency (AMA).

Implications for the public

Since 2009, the African Medicines Regulatory Harmonisation (AMRH) Initiative has made significant gains in strengthening national regulatory systems and harmonising regulatory requirements to bring needed, quality-assured medicines to the African people. However, as the COVID-19 public health emergency highlighted, achieving the expedited regulatory review of medicines and vaccines is vital to shorten the time to market various life-saving medical products. Work must therefore continue to achieve the objectives of shorter timelines and simultaneous access to various African markets, including the recommendations of this study chiefly, the development of legally binding frameworks for regulatory review and increased reliance and collaboration among African regulatory authorities.

Whilst individual NMRAs in Africa have the opportunity to review products independently, there are currently five major regional initiatives that were designed to bring groups of NMRAs together, in order to expedite patients' access to medicines and make recommendations for registration to the individual NMRAs. However, an NMRA can be involved in more than one regional initiative due to their geographical position. The three major regional initiatives in Africa are ZaZiBoNa, the EAC-MRH and the ECOWAS MRH, which have been evaluated and compared. In these regions, because there is not an established legal framework, the recommendations are not mandated as would be the situation for a centralised procedure. Neither is there mutual recognition, which would be the situation with a decentralised procedure, as is exemplified in the European Medicines Agency (EMA).

The East African Community Medicines Registration Harmonisation Initiative

The EAC MRH initiative was established in 2012 as a 5-year pilot and the first regulatory harmonisation project under the AMRH, with the overarching goal to improve access to quality medicines and to test the feasibility of regulatory harmonisation in Africa.[7] Participating countries were Burundi, Kenya, Rwanda, South Sudan, Tanzania, and Uganda.[8] The beginning model employed by the EAC involved NMRA staff from participating countries travelling to Copenhagen to participate in joint assessment sessions with the WHO Prequalification of Medicines programme.[7] However, this model was later discontinued due to unsustainability and assessment sessions are now held within the EAC region. In the current model employed by the EAC, lead NMRAs are designated for key functions: Tanzania for medicines evaluation and registration, Uganda for good manufacturing practices inspections, Rwanda for information management systems, and Kenya for quality management systems.[7] Therefore, products are submitted to the Tanzania NMRA, which conducts the validation and primary review of the application before presenting it to the joint assessment session, which is attended by a representative from each country for further consideration. Only after a recommendation is issued, will the applicant be expected to submit individual applications for marketing authorisation and a fee to each NMRA.[8] Marketing authorisations are granted individually by each country.

The Tanzania NMRA was the first in Africa to attain maturity level 3 status in the WHO Global Benchmarking Tool (GBT) programme in 2018.[4] Maturity level 3 indicates a stable and well-functioning regulatory system.[9]

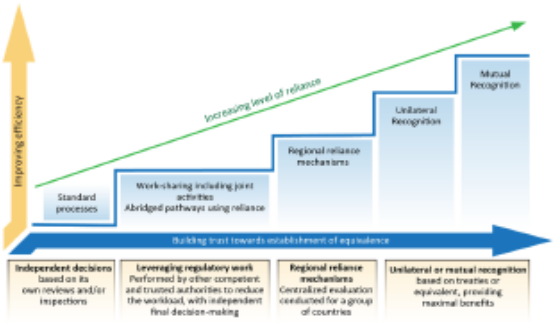

Figure 1. Key Concepts and Levels of Reliance (WHO, 2021).[4]

ZaZiBoNa/Southern African Development Community Medicines Regulatory Harmonisation Initiative

ZaZiBoNa was founded in 2013 by Zambia, Zimbabwe, Botswana, and Namibia to address the challenges of long registration times and inadequate capacity and resources in these countries.[10] In 2015, the SADC MRH project was launched, absorbing ZaZiBoNa. Membership has since grown to include all 16 SADC countries (9 active members, 5 non-active members, and 2 observers). Active member status is determined by the capacity to conduct assessments and good manufacturing practice inspections and the active member countries are Botswana, Democratic Republic of Congo, Malawi, Mozambique, Namibia, South Africa, Tanzania, Zambia, and Zimbabwe.[10] The SADC MRH initiative does not have centralised submissions or approvals/registrations due to the absence of a regional legal framework. In the current model, applicants simultaneously submit applications for registration and pay fees to each of the countries in which they wish to market their medicinal products.[6,10] To be eligible for joint assessment, applications should be submitted to a minimum of two countries. The assessment of dossiers/applications is carried out using a rapporteur and co-rapporteur before consideration of the report by a group of assessors from all the active member countries. Once the evaluation is concluded, an assessment report with a recommendation and a consolidated list of questions is produced and communication of the list of questions to the applicants as well as the final decision on the registration/marketing authorisation of the medicinal products is left to the individual participating countries.[10] Two SADC MRH NMRAs have attained WHO GBT maturity level 3 status, Tanzania, as previously mentioned, and South Africa in 2022.[9,11]

Economic Community of West African States Medicines Regulatory Harmonization Initiative

Similar to other regions in Africa, the ECOWAS region faced challenges in technical capacity and financial resources. In addition, because the ECOWAS region comprises Portuguese-, English-, and French-speaking countries,[12] the differences in official national language further complicated and delayed the implementation of harmonisation. The ECOWAS MRH initiative was launched in 2017 by the West African Health Organization (WAHO) to improve the availability of high-quality, safe and effective medicines and vaccines in ECOWAS.[13] The ECOWAS MRH initiative aimed to reduce the time to registration and improve regulatory oversight through jointly registering locally manufactured and imported medical products.[12] Although the ECOWAS MRH initiative was launched in 2017, joint assessments commenced in 2019 and to date, seven NMRAs; that is, Burkina Faso, Cote d'Ivoire, Ghana, Nigeria, Senegal, Sierra Leone, and Togo have participated in the sessions. Although these seven countries participate in the joint assessments, the outcomes are taken as a basis for the regulatory decision in all 15 NMRAs in the ECOWAS region.[13] In the model employed by the ECOWAS MRH, a country is appointed to serve as lead NMRA/coordinator for two years on a rotational basis. This lead NMRA is assigned to serve as coordinating agency for product applications and is responsible for receiving, validating and preparing applications for review by an assessment team comprising staff from the seven participating NMRAs. The report is then considered during the joint assessment session of the expert working group. The WAHO Secretariat serves as an administrative agency responsible for issuing notifications of recommendations at the regional level. Once this process is completed, each NMRA that receives an application for a jointly reviewed product implements their national procedure to issue a national marketing authorisation. Applicants are given a maximum of two years after the regional review to submit applications for marketing authorisation to countries of their choice. Two ECOWAS NMRAs attained WHO GBT maturity level 3 status Ghana in 2020 and Nigeria in 2022.[11,14]

A common challenge for all three regions implementing harmonisation initiatives was the varying regulatory capacities of participating countries. Barton and colleagues suggested three factors that may be more important: "(1) fragmented and complex drug regulations, (2) suboptimal enforcement of existing regulations, and (3) poorly designed disincentives for non-compliance."[15] To address this issue, capacity building was included in the regional activities to improve standards, build trust and facilitate the proposed harmonisation and reliance initiatives. The AMRH was posited as a precursor to the African Medicines Agency (AMA), which is in the process of being established as a specialised agency of the African Union to improve access to high-quality, safe and efficacious medical products in Africa.[5] It is therefore timely and necessary to conduct a comparison of the existing regional harmonisation initiatives to identify opportunities for improvement and alignment.

Study Objectives

- Compare the operating model, review process and requirements of the three harmonisation initiatives
- Compare the successes and challenges of the initiatives
- Identify opportunities for improvement and alignment of the initiatives and develop recommendations for the way forward.

Methods

Study Participants

All seven members of the EAC MRH (Burundi, Kenya, Rwanda, South Sudan, Tanzania, Uganda, and Zanzibar) as well as all nine active members of the ZaZiBoNa/SADC MRH (Botswana, Democratic Republic of Congo, Malawi, Mozambique, Namibia, South Africa, Tanzania, Zambia, and Zimbabwe) and all seven members of the ECOWAS MRH (Burkina Faso, Cote d'Ivoire, Ghana, Nigeria, Senegal, Sierra Leone, and Togo) participated in the three initiatives that were used for this comparative study. Each regulatory authority was asked to nominate one individual for completing the questionnaire, who had the responsibility for monitoring and documenting regulatory performance metrics.

Content Validity of the PEER Questionnaire

Data were collected in 2021 and 2022 using the Process, Effectiveness and Efficiency Rating questionnaire (PEER)

developed by the authors. In order to further ascertain the content validity of the PEER questionnaire the respondents were asked to answer seven questions with a "yes or no" response options following completion of the PEER questionnaire (Supplementary file 1, Box 1): Did you find the questions clear and straightforward to respond?; Did you find the response options relevant to the heading of each section (A to E)?; Did you find the questions relevant to the aims and objectives of the study?; Did you find the questions relevant to your authority and work-sharing initiative?; Did you find any relevant questions missing? If yes, please state which questions were missing in the space provided after this list of questions; Did you find any questions that should be excluded? If yes, please state the questions that should be excluded in the space after this list of questions; Did you find the questionnaire useful to reflect on both your agency experience as well that of the initiative?

In addition, as part of the cognitive debriefing aspect of the content validity and triangulation of the responses to the PEER questionnaire, semi-structured interviews were carried out with the original survey respondents, and this was designed specifically in order to fulfil the trustworthiness criteria such as credibility, confirmability, dependability and transferability by clarifying respondents' answers and confirming that they had fully understood the questions and their answers.

Furthermore, the rigour and quality of the qualitative part of our study was tested including: credibility, through close and maintained engagement with the respondents (ie, focal person) and triangulation; confirmability, through involving the head of each authority by checking the responses of the "focal person" and the research and keeping notes of the course of events; dependability, through keeping written accounts of the qualitative research process; and transferability, through detailed and comprehensive step-by-step description of the structure and procedure and their operationalisation.[16-18]

to clarify certain answers and confirm that the respondents had fully understood the questions and their answers.

Data Collection

The PEER questionnaire was completed by the focal person/assessor in each country and validated by the head of the authority. The questionnaire comprised five sections under the headings *Demographics*; *Benefits*; *Challenges*; *Improving the performance (effectiveness and efficiency) of the work-sharing programme;* and *Envisaging the strategy for moving forward*. Data were also extracted from the literature.

Based on the synthesis of the results, it was hoped that the authors would generate a series of recommendations, which would then be presented to the regulatory agencies for their endorsement.

The PEER questionnaire was developed and validated by the authors in association with the regulatory authorities specifically for this study. It was piloted with two regulatory authorities in each of three regions who were given the opportunity to comment on the content and the relevance of the questionnaire using a 7-item checklist (Supplementary file 1, Box 1). As part of the relevance aspect of their evaluation they were asked to comment on what was missing and what should be deleted (as not relevant) from the questionnaire. As a result, minor changes were implemented and the final version of the PEER questionnaire was constructed. The study participants were then given two weeks to complete the questionnaire, and two reminders were sent out subsequently so that the data from all participating regulatory authorities were completed within the month after initiation. It was suggested that the questionnaire, which was sent out to the participants by e-mail, could be completed in 15 minutes (average time taken to complete during the pilot) and returned by e-mail as an attachment. Furthermore, we used a triangulation approach in this study, employing multiple methods of data generation including online Zoom virtual interviews in order to ascertain the accuracy of the study participants' responses as well as to develop a comprehensive understanding of the phenomena being explored.

Data Processing and Analysis

The study was exploratory (hypothesis generating) and the nature of the data generated through the PEER questionnaire and the interviews (which were transcribed verbatim) was qualitative. The content analysis technique was used to analyse the qualitative (text) data. The content analysis of the qualitative data employed a conventional approach, using inductive coding based on the data, from which a set of cohesive themes were then generated.

An initial meeting (TS, NN, MOS, SW, and SS) was conducted to examine the content of the data collected and identify initial concepts across the different forms of data collected. Data in the form of key phrases, statements, lists, were independently extracted from the PEER Questionnaire and transcribed texts. A thematic analysis was undertaken where three members of the core team (TS, NN, and MOS) familiarised themselves with the different forms of data and added initial codes.[19] Constant comparison across the different forms of data informed an initial thematic framework to enable consistent coding of the data. If themes were identified from the data that did not fit the initial coding framework, a new code was established to involve the theme in the analysis.

The researchers (TS, NN, and MOS) worked independently to identify themes, but met to discuss the themes and establish consensus. All themes, particularly where consensus could not be achieved, were further discussed and agreed with the rest of the research team (NN, MOS, and SW). This enabled analysis codes to be modified as new ideas were developed.[19] All members of the core research team (TS, NN, MOS, SW, and SS) then commented on the proposed themes and supporting evidence. Reliability was therefore established through discussion, and findings were based on researcher agreement.[20,21]

Descriptive statistics such as frequency were used to analyse the nominal data.

Results

Study Participants Characteristics and Response Rate

Each regulatory authority nominated a focal person who was responsible for measuring and monitoring regulatory performance of their respective region. Each focal person

from the seven members of the EAC MRH (Burundi, Kenya, Rwanda, South Sudan, Tanzania, Uganda, and Zanzibar) as well as all nine active members of the ZaZiBoNa/SADC MRH (Botswana, Democratic Republic of Congo, Malawi, Mozambique, Namibia, South Africa, Tanzania, Zambia, and Zimbabwe) and all seven members of the ECOWAS MRH (Burkina Faso, Cote d'Ivoire, Ghana, Nigeria, Senegal, Sierra Leone, and Togo) completed the PEER questionnaire and took part in the interview, resulting in a 100% (ie, 23 respondents) response from each of the regions.

Part I: Requirements and Review Process

A comparison of the three harmonisation initiatives was conducted (Table).

Type of Procedure

The EAC MRH employs a decentralised procedure in which the applicant does not have the flexibility to choose the country to act as lead NMRA or reference member state for their application. The lead NMRA for all applications submitted to the EAC MRH is the Tanzania NMRA. In comparison, the ZaZiBoNa/SADC MRH employs a hybrid of the decentralised and centralised procedures in that the submission and final approval of applications are decentralised, while the review or assessment is centralised with the implementing NMRA; that is, Zimbabwe, serving as a coordinating agency that assigns applications to a rapporteur and co-rapporteur. Similarly, the ECOWAS MRH employs a hybrid of the centralised and decentralised procedures in that the process begins with a

Table. Comparison of the Review Process and Requirements for MRH of the EAC, ZaZiBoNa/SADC and ECOWAS Initiatives

	EAC-MRH	SADC MRH/ZaZiBoNa	ECOWAS MRH
Type of procedure	Decentralised; however, there is no flexibility in selection of lead NMRA which is the equivalent of the Reference Member State and the EAC Secretariat serves as an administrative agency	Hybrid of decentralised and centralised; implementing NMRA serves as a coordinating agency	Hybrid of centralised and decentralised procedure; WAHO Secretariat serves as an administrative agency and the lead NMRA serves as coordinating agency
Legally binding framework	None	None	None
Eligibility criteria for joint review	Previous intention to market in all participating countries, currently minimum of 2 countries	Submission to a minimum of 2 countries	None, as the regional review precedes national submissions; however, applicants are encouraged to market their products in all 15 countries
Submission windows	No windows; open throughout the year	No windows; open throughout the year	Four 30-day submission windows (Feb, May, Jul, Oct)
Submission of applications	Submission to the lead NMRA then submission to the remaining countries of interest immediately once the regional joint review is completed	Submission to all countries applicant is interested in marketing the product before the regional joint review commences	Submission to lead NMRA based on published expression of interest after a pre-submission meeting, then submission to the remaining countries of interest within 2 years of the regional joint review being completed
Assessment/ review process	Primary and peer review by lead NMRA, peer and final review at joint assessment sessiPrimary review by rapporteur selected using applicable criteria, peer review by second country (co-rapporteur), final review at joint assessment session	Primary review by assessment team, peer and final review by expert working group at joint assessment session	
Communication with sponsors	Responsibility of EAC Secretariat	Responsibility of each individual country to which the application was submitted	Responsibility of WAHO Secretariat
Final approval and marketing status	Approval issued by each individual NMRA in receipt of application and marketed only in those countries	Approval issued by each individual NMRA in receipt of application and marketed only in those countries	Approval issued by each individual NMRA in receipt of application and marketed only in those countries
Target timelines	315 days including applicant's time from the date validation is completed to the date of regional recommendation	270 days including applicant's time (from the date validation is completed to the date of regional recommendation	226 days including applicant's time (from the date validation is completed to the date of regional recommendation)
Target timeline for registration by NMRA after a regional recommendation	90 days	90 days	90 days
Fees	Paid to each individual NMRA; however, there are plans to pilot an additional regional fee	Paid to each individual NMRA; however, there are plans to pilot an additional regional fee	Regional fee paid to the WAHO Secretariat and the lead NMRA and a national fee paid to each NMRA where a national application is made

Abbreviations: EAC, East African Community; ECOWAS, Economic Community of West African States; MRH, Medicines Regulatory Harmonisation; NMRA, national medicines regulatory agencies; SADC, Southern African Development Community; WAHO, West African Health Organization.

centralised joint regional review coordinated by the lead NMRA (currently Nigeria and rotated on a 2-year basis) and supported administratively by the WAHO Secretariat. The process is then decentralised, with each NMRA implementing a national procedure to issue national marketing authorisation upon receipt of applications for the jointly reviewed products.

Legally Binding Framework

The EAC MRH, ECOWAS MRH, and ZaZiBoNa/SADC MRH all do not have legally binding frameworks; therefore, approvals are issued at country level and the products can only be marketed in those specific countries.

Eligibility Criteria

The ECOWAS MRH does not have eligibility criteria because the regional review precedes national submissions; however, applicants are encouraged to market their products in all 15 countries, whereas for the EAC MRH and ZaZiBoNa/SADC MRH, the eligibility criteria is submission (or intention to submit for EAC MRH) to a minimum of two countries to be considered for joint regional review.

Submission Windows

The EAC MRH and ZaZiBoNa/SADC MRH are open for submission of applications all year round, while the ECOWAS MRH accepts applications in four windows each year; that is, February, May, July, and October for 30 days.

Submission of Applications

For the EAC MRH and ECOWAS MRH, applications are submitted to the lead NMRA first then to the remaining countries of interest once the assessment is completed. For the ZaZiBoNa/SADC MRH, applications are submitted only to countries where the applicant is interested in marketing the product.

Assessment/Review Process

The primary review and peer review of applications submitted to the EAC MRH is conducted by the lead NMRA before a final review by all seven EAC countries at a joint assessment session, while for the ZaZiBoNa/SADC MRH, the primary review and peer review is conducted by a rapporteur and co-rapporteur assigned for that particular application before a final review by all nine active member states at a joint assessment session. For the ECOWAS MRH, the primary review is conducted by an assessment team constituting the seven ECOWAS MRH countries before a peer and final review by the expert working group at a joint assessment session of the seven participating countries.

Communication With Sponsors

The responsibility for communication with applicants lies with the EAC Secretariat for the EAC MRH and the WAHO Secretariat for the ECOWAS MRH. For the ZaZiBoNa/SADC MRH, communication with applicants is carried out by each individual country to which the application was submitted.

Final Approval and Marketing Status

The final approval is issued by each individual NMRA in receipt of the application and marketed only in those countries in all three regions.

Target Timelines

The target timeline for the EAC MRH from the date validation is completed to the date of final regional recommendation is 315 days, inclusive of the applicant's time. Applicants are then expected to immediately submit applications to the countries in which they wish to market their products and be issued with a marketing authorisation within 90 days from the date of the regional recommendation. The ECOWAS MRH has a similar process and the target timeline from the date validation is completed to the date of final regional recommendation is 226 days inclusive of the applicant's time. Applicants are then given up to 2 years to submit applications to the countries in which they wish to market their products. The target time for the countries to issue a marketing authorisation once they receive an application is within 90 days. The target timeline for ZaZiBoNa/SADC MRH from the date an application is first discussed at an assessment session to the date a final regional recommendation is given is 270 days, inclusive of the applicant's time. Since the applications are submitted to each individual country in which the applicant wishes to market their products before the joint review, countries are expected to issue the marketing authorisation within 90 days of the regional recommendation.

Fees

Fees are paid to the individual NMRA for registration in each country of interest in all three initiatives. In the ECOWAS MRH, this is preceded by payment of a regional fee to the WAHO Secretariat for the regional review. There are plans to pilot a regional fee in both the EAC MRH and ZaZiBoNa/SADC MRH in the near future. The regional application fees are intended to be used to finance joint reviews in addition to other sources of income, such as partners' support and self-funding by the participating countries in some of the regions.

Part II: Successes

For the comparisons in this section, a vote by the majority of countries (>50%) in a region is recorded as a vote by the region.

There is agreement in the three MRH initiatives about the following strengths of the MRH program; harmonisation of registration requirements across the region, information sharing among regulators and the building of capacity for assessments. However, leadership commitment / governance structure, clear operating model and shorter timelines for approval were identified as strengths only by the EAC MRH (Figure 2).

In all three initiatives, the review of MRH initiative products is prioritised and Committee meetings held regularly enable the timely finalisation of products after an MRH recommendation. These are the strengths of the country processes in the majority of countries. However, none of the MRH initiatives have a list of the products approved using

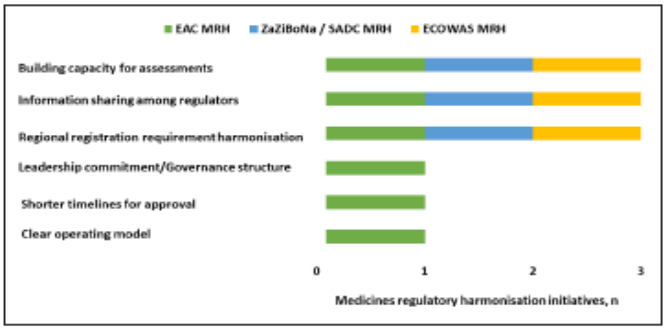

Figure 2. Strengths of the Medicines Regulatory Harmonisation Initiatives. Abbreviations: EAC, East African Community; ECOWAS, Economic Community of West African States; MRH, Medicines Regulatory Harmonisation; SADC, Southern African Development Community.

joint reviews available on the individual country websites and only ZaZiBoNa/SADC MRH have information on the submission process and timelines for MRH products available on the majority of individual country websites as well as a separate register and tracking of MRH products (Figure 3).

Medicines Regulatory Harmonisation Benefits to Member Countries (Regulators)

There is consensus from all three MRH initiatives on the benefits received by member countries (regulators) from participating in the MRH programme and these are the training, which has improved the performance of the assessors, enabling the application of high standards of assessment regardless of the size of the country or maturity of the regulatory authority. This platform has also made it easier for information and knowledge exchange among the countries. However, only EAC MRH were of the view that the shared workload resulted in shorter timelines for approval compared with the individual timelines of the majority of EAC countries.

Medicines Regulatory Harmonisation Benefits to Manufacturers (Applicants)

There is agreement in all three regions about the benefits of the MRH programme for manufacturers/applicants and these are the reduction of the burden of preparing multiple dossiers, as under the MRH programme, only one dossier (modules 2 -5) is compiled for submission to multiple countries. Other benefits are the saving in time and resources, as applicants receive the same list of questions from multiple countries enabling compilation of a single response package as well as simultaneous access to various market. However, only the EAC MRH were of the view that applicants benefited from shorter timelines for approval under the MRH programme compared with the individual timelines of the majority of EAC countries.

Medicines Regulatory Harmonisation Benefits to Patients

The consensus amongst the three regions was that the MRH programme has resulted in quicker access and increased availability of quality-assured medicines for patients; however, this was not at a reduced price.

Part III: Challenges

For the comparisons in this section, a vote by the majority of countries (>50%) in a region is recorded as a vote by the region.

There was consensus amongst all three regions that the lack of centralised submission and tracking was a weakness of the MRH initiatives. The dependence on the countries' processes for communication with applicants and expert committees and the lack of jurisdiction power (the ability to mandate registration) were also identified as weaknesses by the EAC MRH and ZaZiBoNa /SADC MRH (Figure 4).

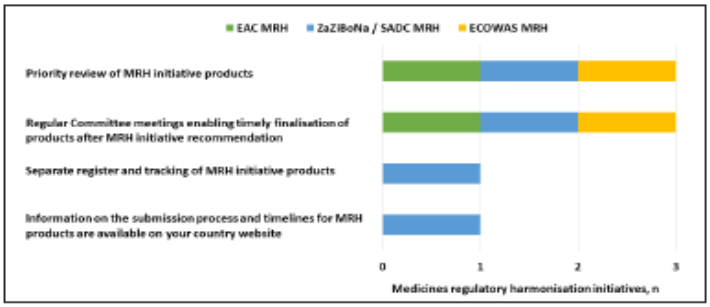

Figure 3. Strength of Country Processes in Implementing the Medicines Regulatory Harmonisation Programme. Abbreviations: EAC, East African Community; ECOWAS, Economic Community of West African States; MRH, Medicines Regulatory Harmonisation; SADC, Southern African Development Community.

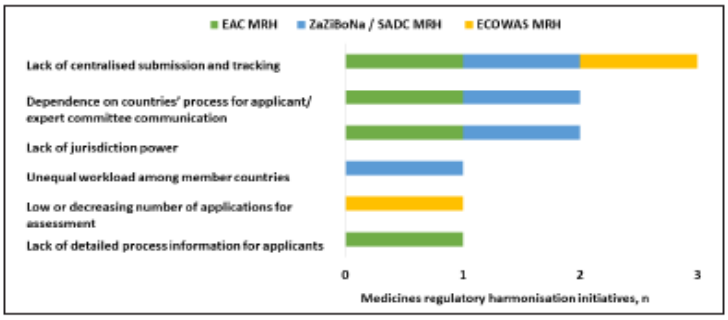

Figure 4. Weaknesses of the Medicines Regulatory Harmonisation Initiatives. Abbreviations: EAC, East African Community; ECOWAS, Economic Community of West African States; MRH, Medicines Regulatory Harmonisation; SADC, Southern African Development Community.

Challenges Faced at Country Level in Implementing the MRH Programme

The three initiatives unanimously agreed that a challenge in implementing the MRH programme is inadequate human resources. Failure by manufacturers to follow the requirement to submit the exact same dossier to all countries of interest and to adhere to deadlines for responses to questions were additional challenges faced by the EAC MRH and the ZaZiBoNa/SADC MRH.

All three initiatives were of the view that a challenge faced by applicants is that the MRH process is more stringent than some country processes. Additional challenges faced by applicants identified by two of the three MRH initiatives were differing labelling requirements in participating countries, lack of information on country websites and the MRH website about the process, milestones, timelines and pending and approved products and a lack of clarity about the process for submission and follow-up in each country (Figure 5).

Accessibility and Affordability of Medicines

An interesting finding from this study was the consensus amongst the three regions that although the MRH programmes had resulted in quicker access and increased availability of quality-assured medicines for patients, this was not necessarily at a reduced price. This could be because most of the regulatory authorities participating in these initiatives are not responsible for regulating the pricing of medicines; moreover, there are no health technology assessment agencies in these countries to perform this function as is the practice in other jurisdictions.[22] As a result, the harmonisation of requirements and work sharing has not resulted in the availability of medicines at a lower price for patients; however, one way the regions plan to negotiate lower prices for medicines is through the implementation of pooled procurement.

Recommendations

The following recommendations are based on the synthesis of the results by the authors, which were then endorsed by the regulatory authorities.

- *Aligning the operating models to improve efficiency*: The EAC MRH and ZaZiBoNa/SADC MRH should consider developing a framework to enable a centralised regional submission and review prior to submission to the individual countries of interest for registration as is the situation in the ECOWAS MRH. In addition, the two-year period given by the ECOWAS MRH for applicants to submit applications to the country after a regional review needs to be revised to align with the other two regions, EAC MRH and ZaZiBoNa /SADC MRH, in which registration in the individual countries is pursued immediately after the regional review.
- *Legal framework*: All three initiatives should consider using three routes/procedures for the approval of

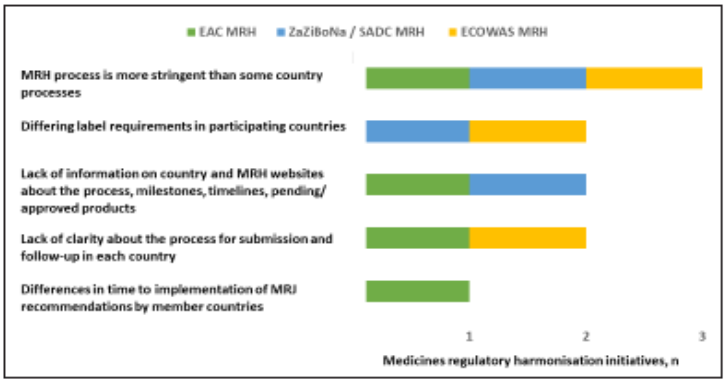

Figure 5. Challenges Faced by Applicants Submitting Applications to the Medicines Regulatory Harmonisation Initiatives. Abbreviations: EAC, East African Community; ECOWAS, Economic Community of West African States; MRH, Medicines Regulatory Harmonisation; SADC, Southern African Development Community.

medical products in their regions; that is, a fully centralised procedure, a decentralised procedure and a national procedure. For all three regions, this would entail pursuing the development of a regional legally binding framework, if possible, to allow the establishment of a centralised procedure.

- *Communication with applicants:* The initiatives implementing any form of a decentralised procedure at submission; that is, EAC MRH and ZaZiBoNa/SADC MRH should communicate with existing and prospective applicants, the target timelines for the joint review process as well as to highlight that the timelines for approval in countries will differ and be dependent on the national process, as it is for other decentralised procedure such as that of the EMA or Australia-Canada-Singapore-Switzerland-United Kingdom Consortium.
- *Publishing an expression of interest:* The EAC MRH and ZaZiBoNa/SADC MRH should implement the practice of publishing an expression of interest as is the situation by the ECOWAS MRH.
- *Information management systems:* In the absence of legally binding frameworks, the regional economic communities (RECs) should invest in robust information management systems to address the weaknesses and challenges identified in this study such as the poor tracking of products and monitoring of timelines in the countries after a joint review is completed.
- *Reliance:* The RECs should continue to support and advocate the strengthening of the capacity of their member states using the WHO GBT assessments and other tools such as Optimising Efficiencies in Regulatory Agencies (OpERA) and Quality of Decision-Making Orientation Scheme (QoDoS) to facilitate inter-country and inter-REC reliance including unilateral and mutual recognition.

Discussion

The AMRH has made significant gains in the strengthening of national regulatory systems and the harmonisation of regulatory requirements since its formation in 2009. According to the regulatory authorities that participated in this study, the three registration harmonisation projects have all managed to meet the core objectives, which were to harmonise guidelines and registration requirements and to build the capacity of member states. The objectives of shorter timelines and simultaneous access to various markets have not been as straightforward to achieve for all the regions, as they are dependent on the time taken by the individual countries to issue a registration/marketing authorisation upon completion of the joint scientific review and in addition for EAC MRH and ECOWAS MRH the time taken by the applicant to submit an application for registration of a jointly reviewed product to the individual countries. The EMA, which has been in existence for over 25 years, provides a blueprint from which the regional harmonisation initiatives in Africa can learn.

Registration or marketing authorisation of a medical product is a legal decision that can only be issued by a legally mandated entity, usually a national regulatory authority within a jurisdiction.[1] As such, networks, organisations or entities without that legal mandate cannot issue a registration. Aware that this limitation existed in the RECs, EAC, ECOWAS and SADC, the regulators decided to establish their work-sharing initiatives as a decentralised model or a hybrid of the decentralised and centralised models, leaving the responsibility for issuing registrations to the national regulatory authorities in their respective countries. This decision has borne fruit, as we report the results of this study show that the initiatives have successfully developed regional guidelines and templates and conducted joint reviews of many products.[8,13,23] The initiatives also resulted in building the capacity of member states; for example, in the EAC, Burundi, Rwanda and Zanzibar were supported in the establishment of semi-autonomous national regulatory authorities that previously did not exist.[24] In SADC, Angola, and Mozambique were also supported in the establishment of semi-autonomous national regulatory authorities. However, there has been some disappointment with the joint review initiatives for the pharmaceutical industry, as their expectation was to have a fully centralised process with a single approval enabling simultaneous access to various markets.[25]

In hindsight, the simultaneous access should not have been promised or expected, as it can only be achieved in a fully centralised process with jurisdiction power, a situation currently not possible due to the founding and operating principles of the RECs. A better approach would have been to communicate the target timelines for the joint review process to applicants from the outset, while highlighting that the timelines for approval in countries would differ and be dependent on the national process as is carried out for the decentralised procedure of the EMA and other similar work-sharing initiatives such as the Australia-Canada-Singapore-Switzerland-United Kingdom Consortium.[26] One initiative that can immediately be implemented to bring alignment in the operating models of the three initiatives and improve efficiency is for the EAC MRH and ZaZiBoNa/SADC MRH to develop a framework to enable a centralised regional submission and review prior to submission to the individual countries of interest for registration, as is carried out in the ECOWAS MRH. In addition, the two-year period given by the ECOWAS MRH for applicants to submit applications to the country after a regional review needs to be revised to align with the other two regions, EAC MRH and ZaZiBoNa/SADC MRH, in which registration in the individual countries is pursued immediately after the regional review. In addition, the lengthiness of this two-year period negates the benefit of shorter registration times that the MRH programme seeks to achieve.

However, it is recommended that all three initiatives consider using three routes/procedures for the approval of medical products in their regions; that is, a fully centralised procedure, a decentralised procedure and a national procedure. For the three regions, this would entail pursuing the development of a regional legally binding framework, if possible, to allow the establishment of a fully centralised procedure as is carried out in the European Union. The use of the centralised procedure could be made mandatory for

certain critical medical products to ensure equitable access in all member states, regardless of regulatory capacity or maturity. The use of regional experts in the assessment of complex products and central safety monitoring is another benefit of a centralised procedure.

Investment in robust information management systems is critical to immediately address the additional weaknesses or challenges identified with the current operating models of the initiatives in this study such as the lack of detailed information for applicants on procedures and the lack of adequate tracking and monitoring of timelines for products in the participating countries once the joint review is completed. This investment will empower the region to publish this information for stakeholders, improving transparency and confidence in the process. This is supported by other studies conducted in these regions, which advocated greater transparency and the use of metrics to identify opportunities to improve efficiency.[27,28]

From the results of this study, it is evident that the countries participating in the three RECs have successfully implemented reliance by leveraging the regulatory work of other NMRAs as well as regional reliance mechanisms. For example, several countries in the RECs have signed bilateral agreements to facilitate the sharing of information for abridged and verification reviews. There is potential for the countries to further implement reliance through unilateral and mutual recognition. Currently, in the East African region, Zanzibar unilaterally recognises the decisions of Tanzania; in the Southern African region, Eswatini, Mauritius and Namibia unilaterally recognise the decisions of South Africa. The regions should continue to support and advocate the strengthening of the capacity of their member states using the WHO GBT assessments (formal and informal). As capacity and trust is built, more countries will consider implementing unilateral and mutual recognition within a region as well as between the different RECs on the continent. In addition, measures should be implemented to increase efficiency in the regulatory review process such as the use of the OpERA tool to track, monitor and evaluate performance.[29] Greater transparency through the publishing of public assessment reports as well as documenting the benefit-risk assessments conducted and the basis for reaching decisions using tools such as the QoDoS will facilitate a greater extent of reliance.[30]

Limitations and Future Work

The scope of this study was limited to the processes and operating models of the regional harmonisation initiatives. In future, it would be helpful to obtain quantitative data to support these views. For example, the specific metrics of the time taken to register the medicinal products in the individual countries after a regional recommendation and the status of commercialisation and pricing of the medicinal products in the individual countries as well as the factors influencing these metrics could be the subject of a future study.

Conclusion

This study has highlighted the successes of the medicine registration harmonisation initiatives in Africa as well some opportunities for improvement and alignment. The results of this comparison allow for the three regional harmonisation initiatives to learn from each other, and the implementation of the recommendations made in this study will bring greater alignment and efficiency in their operating models thereby strengthening the foundation of the soon to be operationalised AMA.

Ethical issues

The study was approved by the Health, Science, Engineering and Technology ECDA, University of Hertfordshire, United Kingdom [Reference Protocol number: LMS/PGR/UH/04988]. Data were managed in compliance with the General Data Protection Regulation and any regulations regarding management of personal data required by participants' respective country of residence. All the national medicine regulatory authorities in East Africa approached to take part in the study were satisfied with ethics approval obtained from the United Kingdom and did not require us to apply for any IRBs in East Africa.

Competing interests

Authors declare that they have no competing interests.

Data Availability Statement

We include a copy of the questionnaire in the Supplementary materials and the raw data will be available on request.

Authors' contributions

TS Devised the study, analysed the data and wrote the manuscript.
NN Provided data and critically reviewed the manuscript.
MO-A Provided data and critically reviewed the manuscript.
SW Devised the study, analysed the data and wrote the manuscript.
SS Devised the study, analysed the data and wrote the manuscript.

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Supplementary files

Supplementary file 1 contains Box 1.

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Evaluation of Good Review Practices in member agencies of the East African Medicines Regulatory Harmonisation Initiative: Strategies for Alignment with African Medicines Agency

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Running title: Good Review Practices of NRAs in EAC.

Introduction

The East African Community (EAC) Medicines Regulatory Harmonisation (EAC-MRH) programme was established to address the medicines regulatory challenges faced by the regulatory authorities of the region. Work sharing through joint assessments and inspections was adopted as an effective way to manage the limited resources and capacity while ensuring patients' timely access to medical products. However, the capacity and review practices of these agencies are also a key determinant to the success of the joint work. Faster registration of medicines even after a regional recommendation has been made, depends on the decision-making processes of the National Regulatory Authorities (NRAs). This study is therefore aimed to evaluate Good Review Practices (GReVP) in the agencies participating in the East African Medicine Regulatory Harmonisation Initiative and map the strategies as the countries align themselves with the African Medicines Agency (AMA).

Methods

A validated questionnaire which standardises and captures review processes was completed by the Head of the medicines registration division in each of the seven NRAs. A country report based on the completed questionnaire was developed for each NRA. These reports were then validated by the heads of the respective agencies.

Results

The population and size of the regulatory agencies in the seven countries in the region vary. On governance, four of the countries have semi-autonomous agencies while three have autonomous agencies. On the source of funding, the Burundi and South Sudan agencies were fully funded by their governments, entirely from fees for Kenya and Uganda agencies, while Rwanda, Tanzania and Zanzibar were partially funded from different sources. All the six agencies apart from South Sudan who does not receive, or review applications had backlogs. The fees charged by the agencies varied based on the different kind of application categories received (New chemical Substances, biologicals, and generics). The key milestones for standardized regulatory processes are implemented in all the agencies with some differences identified. Queue times are different ranging from a few weeks in some agencies to about one year in others. Three of the agencies use internal technical agency staff for scientific assessments while three use both internal and external experts for the primary scientific assessments. The clock stop time varies from agency to agency. Target timelines for the start and finish for the review committee vary from one day (Tanzania), one month (Uganda) to three months (Burundi). Kenya does not have a target timeline for the committee. All the agencies are implementing some best practices on quality measures, transparency and communication. Some have activities for transparency improvement but with minimal attention to training and education. Most of the agencies have some measures in place for quality decision-making practices.

Conclusion

The Good Review Practices (GReP) of these agencies participating in the East African Medicine Regulatory Harmonisation Initiative still needs to be improved. This is a baseline study and has demonstrated how the EAC-MRH perform regulatory reviews as one of its objectives to improve capacity of NRAs. It is imperative that these countries streamline and harmonise their practices. Increasing human resources and an investment in training and education of staff will enable the implementation of all measures for GReVP. The effectiveness and efficiency of the AMA will depend on the strength of these NRAs.

Key Words: EAC Joint Assessment Procedure; Good Review Practices; Regulatory Reliance

INTRODUCTION

The East African Community (EAC) is made up of seven countries: the Republics of Kenya, Uganda, Rwanda, Burundi, South Sudan, the Democratic Republic of Congo (DRC) and the United Republic of Tanzania. The DRC was recently admitted in 2022 after this study had been conducted. This intergovernmental organisation with a population of 303,397,152 has its headquarters in Arusha, Tanzania. The countries in this region have common medicines regulatory challenges such as differences in countries' laws and regulations, inadequate

capacity with the National Medicines Regulatory Authorities (NRAs) of the region (Kamwanja, 2010 and Mashingia et al 2020). To address these challenges, the EAC Secretariat in collaboration with the EAC NRAs established the East Africa Medicine Harmonisation Project (EAC-MRH) in 2012 as the regional coordinating body of the AMRH Initiative. This was part of the implementation of one of the provisions of the EAC Treaty, Chapter 21, Article 118 on regional harmonisation in health (EAC Compendium, 2014).

Operational aspects of EAC-MRH

The East African Community (EAC-MRH) is one of the five regional medicines regulatory harmonisation programmes in Africa. There are seven national medicines regulatory authorities (NRAs) of the region participating in the EAC-MRH initiative. These countries share a common history, market, language, culture, and already had a treaty that called for these countries to harmonise. The aim of the programme since its inception was to reduce registration timelines of medical products through joint reviews and joint inspections with an overall goal to enhance access to safe, efficacious and quality medicines by patients in the region. Through harmonisation and work sharing for about ten years, 25 joint assessments have been conducted with about 202 products reviewed and 107 recommended for registration by the EAC Partner States (Ngum et al, 2023). However, due to the long bureaucratic process for the review and approval of the official notification letters to applicants, the median time for the communication of approval to the applicant following the scientific assessment generally exceeded the EAC target of 30 calendar days (Mashingia et al, 2023). Also, one of the key challenges faced by the work sharing initiative is delay in granting marketing authorisation (MA) by the NRAs. The NRAs have varying timelines for products to be registered at national level after a regional recommendation is made (Ngum et al, 2023). According to Mashingia et al (2023), the EAC target time for granting the MA of 116 calendar days was far exceeded by all five authorities. The median times for granting MA by Burundi (ABREMA), Kenya (PPB), Rwanda FDA, Uganda (NDA), and Tanzania (TMDA) were 965, 683, 649, 582, and 515 calendar days, respectively. Several reasons have caused the long median times to grant the MA by the EAC NRAs; long administrative procedures, such as NRA requirements for product applications to be considered first by the scientific committee before a certificate of MA could be issued; delays by applicants in paying fees for registration after filing for MA in NRAs; NRAs in the region are operating at different maturity levels with limited capacities and capabilities to conduct timely scientific reviews with applicants expected to pay varying amounts for fees in the different NRAs (Table 1).

This study is therefore aimed to evaluate Good Review Practices (GReVP) in the agencies participating in the East African Medicine Regulatory Harmonisation Initiative and map strategies for moving forward as they are going through the process of alignment for the operationalisation of the African Medicines Agency (AMA). This is the first in a two-part series and the second article will focus on the review models and timelines of these agencies.

MATERIALS AND STUDY PARTICIPANTS

Study Participants

The study participants included Senior Programme Officers heading the Medicines registration divisions in the seven NRAs; Pharmacy and Poisons Board-PPB, Kenya; National Drug Authority-NDA, Uganda; The Tanzania Medical Devices Authority (TMDA);

Zanzibar Food and Drugs Authority (ZFDA) Tanzania; Drug and Food Control Authority – DFCA South Sudan; Burundi Food and Medicines Regulatory Authority (ABREMA) and the Rwanda Food and Drugs Authority.**Data Collection**

A validated questionnaire describing the organisation structures, regulatory review systems for market authorisation of new active substances (NAS's) and generics including their overall timelines from the date of submission of the application to when it is approved, good review practices (GReVP) and quality decision making practices, was completed by each of the agencies in 2022. The questionnaire was composed of six different parts: *Part 1* - Organisation of the agencies with focus on its structure and resources; *Part 2* – types of review models used by the agencies for scientific assessment of medicines; *Part 3* - key milestones in the review process with focus on the process map and milestones; *Part 4* – good review practices (GReVP) and how the agencies build quality into their regulatory processes; *Part 5* - quality of the decision-making processes based on whether the agencies have good measures in place to guide decision making; and *Part 6* – was based on concluding observations that relate to the strengths and challenges for the agencies to carry out its mandate.

RESULTS

For the purpose clarity, the results of this first article of the series will be presented in four parts: Part 1- Organisation of the regulatory authorities; Part II - Key Milestones in the review process; Part III - Good Review Practices; Part IV - Quality Decision-Making Practices.

Part 1: Organisation of the Regulatory Authorities

The population and size of the regulatory agency of the six countries in the region vary (Table 1). The top two countries with the largest population are Tanzania (65.4 million) and Kenya (54.9 million). Four countries (Kenya, Rwanda, Burundi, Zanzibar), have semi-autonomous agencies and operate within the administrative structure of their Health Ministries, while South Sudan, Uganda and Tanzania have autonomous agencies and are independent from their Ministries of Health. Six of the agencies regulate medicinal products, medical devices, and in vitro diagnostics for human and veterinary use and only the Burundian authority regulates medicines for human use and food and not veterinary use.

Most of the staff in the seven agencies were pharmacists Kenya had the highest proportion of reviewers to total agency staff (16%) followed by Tanzania (13%) , Burundi (12.5%), Uganda (11%), South Sudan (10%), Rwanda (8%), Zanzibar (8%). Only Tanzania indicated they used external experts for review of applications for marketing authorisation (Table 1).

If all applications received in 2022 were reviewed, then the number of applications reviewed per reviewer in each of the agencies would be 44 applications by Rwanda FDA, 36 in Kenya PPB, 26 by Uganda, 23 in Burundi (ABREMA), 19 in Tanzania (TMDA) 1 by Zanzibar, and 0 by South Sudan (DFCA). However, all the six agencies apart from South Sudan who does not receive, or review applications, indicated they had backlogs. Therefore, not all the applications received for that year were reviewed within the same period.

Source of Funding

The Burundi and South Sudan agencies were fully funded by their governments. The source of funding for Kenya and Uganda agency was reported to be entirely from fees, while Rwanda, Tanzania and Zanzibar were partially funded from different sources. For Rwanda 22% came

from the government, 76% from fees and 2% donations from partners. For Tanzania, 11.7% government; 76.3% fees; 0.6% development partners and 11.4% balance from previous budget. For Zanzibar, Government provides 49.6%, Fees 41.6% and Donors 8.8%. The fees charged by each agency varied between $500, $1000 to $2000 based on the different kinds of application categories received (New chemical Substances, biologicals, and generics). Kenya charged the lowest fees ($500) for local manufacturers for all categories, while Tanzania charged the highest fees ($3500) for review of biologicals. Burundi and South Sudan agencies do not charge fees for applications for marketing as they are fully funded by government. The Burundi agency however charges fees for some activities such as registration and importation and these fees are put into the national bank and not in the Agency bank account. Each year the Burundi government then gives the Agency a fixed budget for operating costs. (Table 2). Generally, agencies that fully depend on the government as their main source of funding charge less fees as compared to agencies that are fully reliant on fees.

Part II: Key Milestones in the review process

Figure 1 below shows a standardised review process map being implemented in well-resourced regulatory systems with key milestones being recorded after each phase. This process map is a simplified version of the key steps taken during the review of a New Active Substance (NAS) and does not include rejections. The focus here is mostly on products that only go through one cycle of review although it usually will take more than one cycle for most applications to be reviewed and a recommendation made. South Sudan will not be part of the analysis in this section as DFCA is yet to engage in review activities as key points in the review procedure and timelines are not applicable or cannot be confirmed.

Receipt and validation procedure

All agencies indicated that when the application is received, they begin by checking for correctness. If the application is incomplete, the applicant is notified. A time limit which varies across the agencies is given to the applicant to respond. If the timeline is not respected, then the application will be considered as withdrawn. Items checked at this stage may include the legal status of the applicant or local agent; the GMP status of the manufacturer; proof that correct fees have been paid; acceptable format which could include ICH, CTD or local requirement and correct sections of scientific data. It is at this point where the agencies decide the kind of review pathway that will be conducted (full review, abridged or verification). Successful applications are then placed in the queue for scientific assessments.

Queue time

After completion of the validation process, queue time commences, and this is the time between validation and start of primary scientific assessment. All agencies recorded this milestone but implementing different queue times ranging from a few weeks in some agencies to about one year in others. Tanzania (2 to 8 weeks), Burundi, Rwanda (2 to 6 months), Zanzibar (60 to 180 days), Uganda (12 months), for Kenya (more than one year). Priority products are not included in the queuing system.

Primary Scientific Assessment

Milestone 3 is the start of the scientific assessment which was recorded by all the six agencies. Rwanda, Zanzibar, Burundi use internal technical agency staff for scientific assessments while

Tanzania, Kenya, and Uganda use both internal and external experts for the primary scientific assessment and detailed assessment report, recommendations and clinical opinion respectively. Four of the agencies indicated that scientific data being reviewed in their agencies is categorized into quality, safety and efficacy except for Burundi and Uganda who do not separate although quality, safety and efficacy are reviewed in this sequence by these agencies.

Questions to Applicants

All six agencies indicated that no meetings can be held by sponsors with the agency staff to discuss any queries emanating from the assessment. Rather, the questions are consolidated into a single batch and sent to the sponsor. At this stage, the clock stops for Kenya, Burundi, Zanzibar and Tanzania as the applicant is given time to respond. The clock stop time varies from agency to agency. However, Uganda and Rwanda do not stop the clock while questions are being answered by the applicant.

Review by Experts Committees

Five of the agencies engage a committee of experts in the review process. These experts are consulted after the agency has reviewed and reported on the scientific data. Target timelines for the start and finish for the committee vary from one day (Tanzania), one month (Uganda) to three months (Burundi and Zanzibar). Kenya does not have a target timeline for the committee. The report from the committee is presented to the board in most of the agencies for review. In some of the agencies (Burundi, Rwanda) they are mandated to follow the committee's recommendations, but other agencies are not mandated to do so (Uganda, Kenya, Tanzania).

Authorisation Procedure

Three of the NRAs (Kenya, Zanzibar and Uganda) inform their sponsors of a positive scientific opinion before the authorisation is issued, while the other three NRAs (Burundi, Tanzania and Rwanda) do not.

Part III: Good Review Practices

Quality Measures

A comparison of the quality measures implemented by the seven regulatory authorities is illustrated in Table 3. Kenya, Rwanda and Tanzania implemented all the eight quality measures while Uganda implemented 6, Zanzibar 4 and Burundi 5 out of eight. All the agencies implemented good review practices and used the scientific expert committees. Only Uganda indicated that they did not have standard operating procedures and Burundi did not have assessment templates in place. On the internal quality policy, all NRAs except Burundi are implementing this. Except for Uganda and Zanzibar all four NRAs have dedicated quality departments. All six NRAs participated in shared and joint reviews. South Sudan did not implement any of the measures possibly because they are not reviewing any products currently.

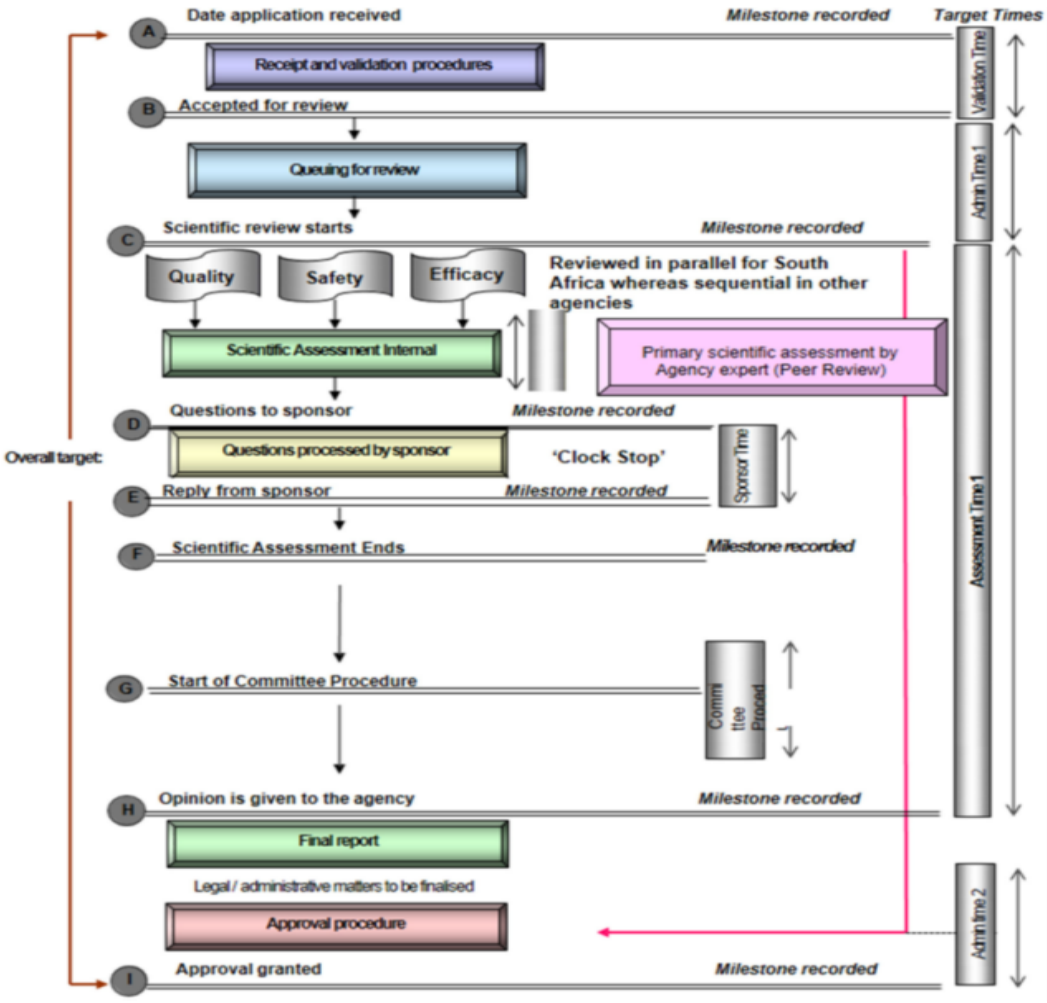

Figure 1: Standardised process map for the review and approval of medical products (adopted from Sithole et al, 2021)

Transparency and communication

On assessing the implementation of nine best practices on transparency and communication (Table 4), all six agencies reported that they have in place official guidelines to assist industry and a list of approved products that allow for industry to track progress of their applications via email and telephone. Three agencies did not provide post-approval feedback to applicants on the quality of the submitted dossiers. Only two agencies (Rwanda and Uganda) provided details of technical staff to contact during the review of applications and only one country (Uganda) publishes the advisory committee meeting dates. Three agencies namely Kenya, Uganda and Tanzania reported that they do publish summary of assessment reports on which the approval was granted.

Continuous improvement initiatives

Five areas (external and internal quality audits; internal tracking systems, reviews of assessors' and stakeholders' feedback), were assessed to determine continuous improvement initiatives in the six regulatory authorities (Table 5). Tanzania implemented all five initiatives, while Uganda Kenya and Zanzibar implemented four out of the five initiatives. Rwanda implemented three and Burundi implemented two out of five.

Training and Education

The following measures were assessed that contribute to the development of staff and the efficiency of the regulatory review process, through training and education; training programme for assessors, international workshops, external courses, in-house courses, on the job training, external speakers invited to the authority, induction training, sponsorship of postgraduate degrees, placements and secondment in other regulatory authorities. All six countries implement most of such measures. However, Burundi, Kenya and Uganda did not have a policy in place to invite external speakers to the authority, Burundi and Rwanda did not sponsor postgraduate degrees; Uganda reported that they do not host international workshops or conferences and along with Burundi and Rwanda do not make placements and secondments in other regulatory authorities.

Part IV: Quality Decision-Making Practices

Ten quality decision-making practices were used to determine whether these agencies have measures in place to ensure that quality decisions are made using the data submitted during the review of applications. Out of the ten quality decision-making practices, Kenya implemented four, Rwanda eight, Zanzibar three, Uganda five, Burundi eight and Tanzania implemented all the ten quality practices.

DISCUSSION

The aim of this study was to evaluate Good Review Practices (GReVP) in agencies participating in the East African Medicine Regulatory Harmonisation Initiative and map strategies aligning with the African Medicines Agency. Comparing the similarities and differences of agencies in this region will assist them through information sharing to identify best practices in the process and documentation of the review procedures. It will also assess how these agencies build quality into their review processes. Ensuring standardisation, improvement in documentation, timeliness, predictability, consistency and high quality of reviews and review reports will entail efficient and effective GReVP in regulatory agencies (Reference). One of the key challenges faced by industry in applying for marketing authorisation has been the lack of detailed information (Ngum et al, 2022) on the regulatory procedures for applicants. This study which is similar to one conducted by Sithole et al, (2021) for the SADC region will raise awareness to industry as well as applicants on the regulatory processes for each agency. This will enhance transparency and clarity on the application process thereby leading to an increase in investments in medicines development and improved submission of applications to agencies in the region.

As a result of the participation of all the EAC agencies in the regional harmonisation initiative, they are now operating either as autonomous (3 agencies) or semi-autonomous agencies (4

agencies). This has therefore improved the regulatory review processes of these agencies. One of the key challenges for regulatory systems strengthening in most countries in Africa is the absence of an autonomous National Medicines Regulatory Authority (NRAs) mandated to regulate the market. In countries where regulatory functions are split among two or more agencies, there is usually duplication of effort, lapses in implementation, inconsistencies and spreading of limited resources too thinly. With autonomous agencies, efficiency and effectiveness can be ensured as this governance structure enables the agency to focus on regulation (Dube-Mwedzi1et al, 2020). The African Union Model Law on medical products regulation (AU Model Law) provides for the establishment of autonomous NMRAs for effective coordination and regulation of medical products in a country. However, article five of the AU Model Law recommends that agencies should be fully autonomous. This law was endorsed by the Heads of States and Governments in 2016 (Ncube et al, 2023) whose objective is to promote collaboration across countries and provide an enabling environment for the manufacturing, testing and scaling up of essential and priority medical products in Africa. Five out of the six countries in the region have comprehensive legal frameworks thereby providing a good foundation for effective regulation (Ndomondo-Sigonda et al, 2021).

Challenges of human resource constraints are faced by all the agencies as they all had backlogs during the period of the study. Even though one of the strengths of the EAC-MRH initiative has been building the capacity of assessors in the region (Ngum et al, 2022), there is still a significant gap in terms of numbers of assessors in these agencies as per the results of this study. Strengthening of the harmonisation initiative, operationalisation of the African Medicines Agency and reliance on well-resourced agencies by less resourced agencies are being proposed as some of the immediate interventions to address the challenge of limited resources (Ngum et al, 2022 and Shabani et al, 2022). However, the results of this study demonstrate that the NMRAs receiving the highest number of applications (Tanzania, Kenya, and Uganda) use both internal and external experts for the primary scientific assessment while the NRAs with less applications for review utilise only their internal technical agency staff for scientific assessments.

One of the major challenges observed in this study is the recording of the timelines for each milestones achieved. These all vary amongst the NRAs in the regions with most agencies not implementing a routine recording of timelines for key indicators such as timelines for validation. This comparative study will act as a baseline and will assist the NRAs to reflect on their key performance indicators as they build on the continuous monitoring of performance. Assessing the current situation will be a guide for making informed decisions on how to improve performance (Sithole et al, 2021) as countries will learn from each other on how NRAs with similar resources conduct their reviews.

This study is also crucial for the EAC-MRH initiative especially as this relies on country processes to register medical products that have been recommended by the joint review process. The current observation is that countries delay implementing the recommendations from the regional process. It is therefore important for the EAC-MRH program to revise its process to limit dependency on the country processes which are already overwhelmed with the national workload. The understanding of country-specific requirements that follow an EAC-MRH positive opinion to address reasons for further delays in the approval process is key for the alignment to the African Medicines Agency (Ngum et al, 2022).

RECOMMENDATIONS

The following are the recommendations emanating from this study.

1. **Measuring & Monitoring Timelines**. Agencies in the EAC-MRH initiative should implement systems that will enhance the measurement and monitoring of timelines for the key milestones of the registration process such as dates of submission, validation, start of scientific assessment, completion of scientific assessment and registration.

2. **Applicants Communication**. Clear registration processes should be documented and shared with the apllicants as well as publishing timelines, assessment reports, and the summary basis of approval which will facilitate transparency and accountability.

3. **Work-Sharing**. The EAC-MRH should develop measures to mandate the registration of products at a national level following regional recommendation. This approach would ultimately lead to faster availability of medicines to patients as well as reducing demand on capacity.

4. **Quality Decision-Making Practices**. Although all the agencies indicated they are implementing the quality decision making practices, there is still a need for training and education in this area.

CONCLUSION

For the African Medicines Agency to be successful and achieve its objectives, country regulatory processes need to be streamlined and differences in country requirements minimised. Like the EAC-MRH, the AMA will also depend on countries to implement the decisions recommended by this continental body. It is therefore crucial that the groundwork in the operationalisation of the AMA focuses on improving the review practices of the NRAs so as to minimise any delay in granting marketing authorisation to medical products. It is imperative for countries to implement good review practices in order to accelerate patients' access to safe, quality and effective medical products when the African Medicines Agency is established.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study was approved by the Health, Science, Engineering and Technology ECDA, University of Hertfordshire, United Kingdom [Reference Protocol number: LMS/PGR/UH/04988].

AUTHOR CONTRIBUTIONS

NN, SS and SW: Contributed to the design of the study, implementation of the research, analysed the data and drafted the manuscript. EAC focal points contributed to the implementation of the research and critical review of the manuscript. MNS critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

ACKNOWLEGEMANTS

SUPPLEMENTARY MATERIAL

TO BE SUBMITTED TO FRONTIERS IN MEDICINE

Comparison of GReP in EAC countries

Table 1: Size of Agencies

Measure	BURUNDI	KENYA	RWANDA	SOUTH SUDAN	TANZANIA	UGANDA	ZANZIBAR
Population (millions)	13.1	54.9	13.2	11.3	65.4	45.7	1.7
Agency staff	32	170	188	42	336	292	150
Number of internal reviewers	4	28	15	4	45	33	12
Reviewers in Agency staff	12,5	16%	8%	10%	13%	11%	8%
Total applications received	70	997	659	0	858	861	10
Number of applications per reviewer	23	36	44	0	19	26	1

Table 2: Comparison of the fees charged (USD) and source of funding in 2023

Measure	BURUNDI	KENYA	RWANDA	SOUTH SUDAN	TANZANIA	UGANDA	ZANZIBAR
Source of funding	100% Government	100% Fees	Partially funded from different sources 22% Government 76% Fees 2% Donations from partners	100% Government	Partially funded from different sources (11.7% Government; 76.3% fees; 0.6% development partners; 11.4% balance from	100% Fees	Partially funded from different sources: % Government: 49.6% % Fees: 41.6% % Other (Donors): 8.8%

					previous budget		
Total Annual Budget (USD)	400BiF 600.000.000 BIF	13,796,120	9,155,400	8 million SSP (2019-2020)	19,123,740	603,554	US$826,483 (2023)
Fees for review of a new chemical entity (USD)	N/A	1000 international 500 Local		N/A	2000	2000	N/A
Fees for review of biologicals (USD)	N/A	1000 international 500 Local	1250	N/A	3500	2000	2000
Fees for review of generics (USD)	N/A	1000 international 500 Local	1250	N/A	2000	2000	1000

Table 3: Comparison of the quality measures implemented by the seven regulatory authorities.

Quality Measure	**Regulatory Authority**						
	BURUNDI	**KENYA**	**RWANDA**	**SOUTH SUDAN**	**TANZANIA**	**UGANDA**	**ZANZIBAR**
Good review practice system	✓	✔	✔	x	✔	✔	✔
Internal quality policy	✓	✔	✔	x	✔	✔	✔
Standard operating procedures for guidance of assessors	✓	✔	✔	x	✔	x	✔
Assessment templates	✓	✔	✔	x	✔	✔	✔
Peer review (internal)	✔	✔	✔	x	✔	✔	
Dedicated quality department	✓	✔	✔	x	✔	x	✔
Scientific Committee	✓	✔	✔	x	✔	✔	✔
Shared and joint reviews	✓	✔	✔	x	✔	✔	✔

x-not implemented

✓ formally implemented

Table 4: Comparison of the transparency and communication parameters in the six agencies.

Quality Measure	Regulatory Authority						
	BURUNDI	KENYA	RWANDA	SOUTH SUDAN	TANZANIA	UGANDA	ZANZIBAR
Post-approval feedback to applicant on quality of submitted dossiers	✓	✔	x	x	x	✔	✔
Details of technical staff to contact	✔	x	✔	x	x	✔	x
Pre-submission scientific advice to industry	✓a	✔	✔	x	x	✔	x
Official guidelines to assist industry	✓	✔	✔	x	✔	✔	✔
Industry can track progress of applications	✓	✔	✔	x	✔	✔	✔
Publication of summary of grounds on which approval was granted	X	✔	x	x	x	✔	✔
Approval times	✓	✔	✔	x	✔	✔	✔
Advisory committee meeting dates	x	x	x	x	x	✔	x
Approval of products	✓	✔	✔	x	✔	✔	✔

x-not implemented

✓ formally implemented

✓a informally implemented

Table 5: Comparison of continuous improvement initiatives in the six regulatory authorities.

Quality Measure	Regulatory Authority						
	BURUNDI	KENYA	RWANDA	SOUTH SUDAN	TANZANIA	UGANDA	ZANZIBAR
External quality Audits	x	x	x	x	✔	x	x
Internal quality Audits	✓	✔	✔	x	✔	✔	✔
Internal tracking Systems	✔	✔	x	x	✔	✔	✔
Reviews of assessors' feedback	✓	✔	✔	x	✔	✔	✔
Reviews of stakeholders' feedback	✔	✔	✔	x	✔	✔	✔

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APENDIX 2 - Conference Abstracts and Presentations

Abstract submitted for student Poster at DIA Global 2023, Boston, United States of America 25 to 27 June 2023

Title Evaluation of the Effectiveness and Efficiency of ten years' experience with the East African Community Joint Assessment

Track 9: Regulatory or Track 10: Regulatory CMC and product quality

Key words East African Community work-sharing initiative, benefits, challenges, effectiveness, efficiency

Objective

To evaluate the effectiveness and efficiency of the current East African Community Medicines Regulatory Harmonization (EAC-MRH) operating model, from both the regulators and applicants' perspective. This included identifying the benefits, challenges and opportunities for improvement. –

Method

The Process Effectiveness and Efficiency Rating (PEER) questionnaire was used to identify the benefits and challenges for improving the performance of the EAC initiative. This was completed by seven EAC assessors and 14 pharmaceutical companies coupled with Semi-structured interviews.

Results

The East African Community Medicines Regulatory Harmonization (EAC-MRH) regional initiative consists of seven agencies, namely Burundi, Kenya, Uganda, Rwanda, South Sudan, Tanzania and Zanzibar. It has been of considerable value since it was established in 2009 as it moves toward achieving its main objectives of shorter timelines for approval of medicines, information sharing among regulators and capacity building for assessments, resulting in quicker access and increased availability of medicines for patients in the region. Pharmaceutical companies outlined how the initiative has facilitated the harmonisation of registration requirements across the EAC region leading to one registration for all countries and a reduction of the workload for both applicants and assessors. In addition, it is expected that shorter timelines for approval will lead to improved access to quality-assured essential medicines in the region. Access to various markets at the same time was also noted as an important benefit to pharmaceutical companies.

However, the key challenges identified by the agencies in the Region that have hindered the expected effectiveness and efficiency of this initiative were the lack of a centralised submission and tracking system; a lack of mandated registration; inadequate human resources, manufacturers' failure to submit the exact same dossier to all countries of interest; a lack of an integrated information management system; a lack of information on national medicines regulatory authority or EAC websites; and challenges in monitoring and tracking assessment reports.

A key strategy proposed by both agencies and applicants was the establishment of a regional administrative body to centrally receive and track EAC applications and the eventual establishment of a Regional EAC Medicines Authority.

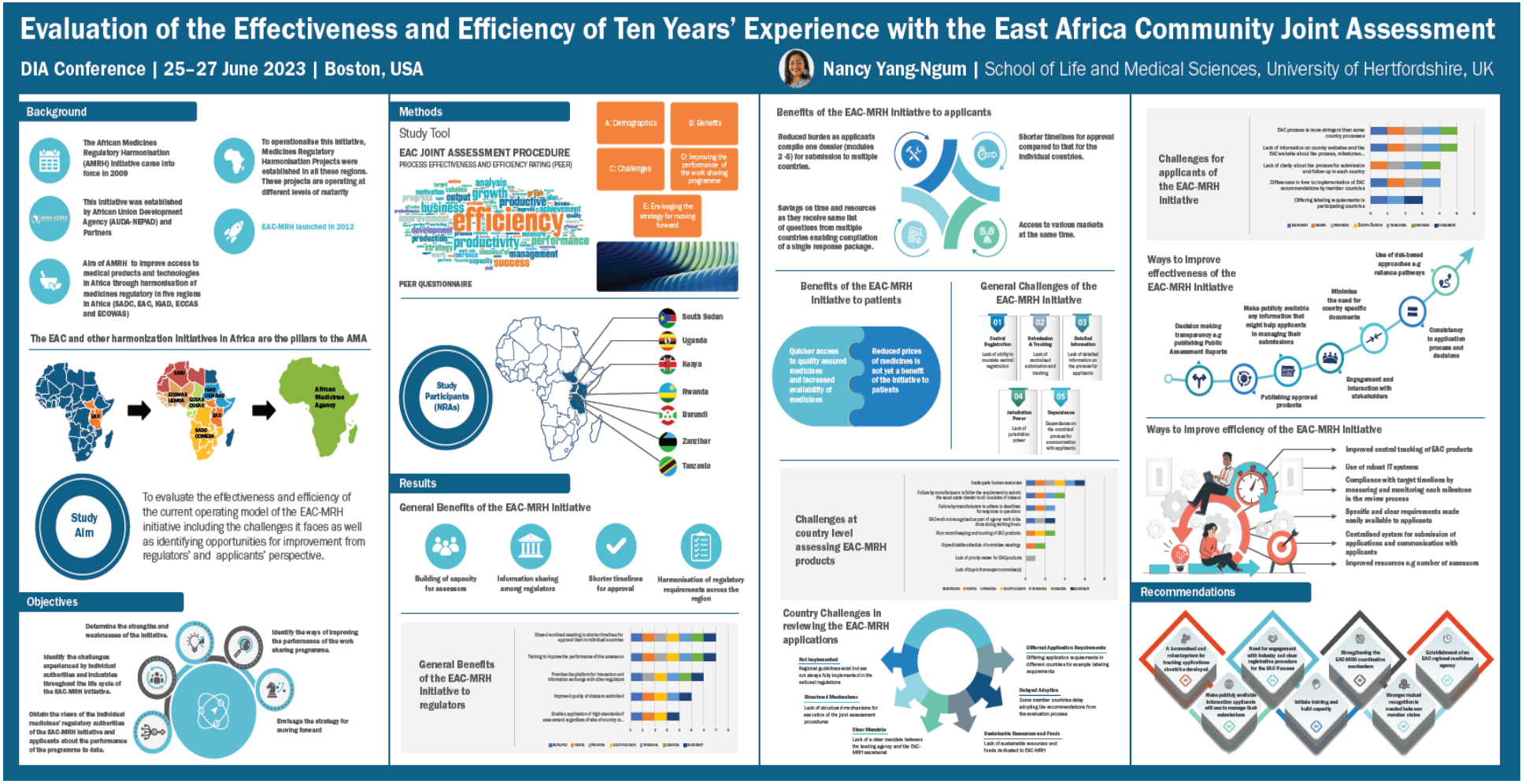
Conclusion

The use of a robust information technology system for the central tracking of EAC products is essential to address the identified challenges and improve regulatory effectiveness and efficiency. To expedite the process and to ensure transparency, information on decision making should be available on national and regional websites. Strategies for enhancement include improving the capacity of assessors, work and information sharing and a coordination mechanism for the regional joint assessment, with the eventual establishment of a regional medicine agency. As this is the first study evaluating the performance of the EAC work sharing initiative, it was believed that the system performs efficiently. However, in some member countries an EAC positive recommendation does not directly result in an individual country approval. If the recommendations are implemented, then this should facilitate the overall goal of the initiative to expedite the availability of quality-assured medicines to patients in the region.

While harmonisation is key to ensuring access to safe, effective, and high-quality medicines, accessibility and affordability also need to be addressed to realise the full benefits of the medicines regulatory harmonisation initiative. Full implementation of the EAC road map 2020–2022 is critical to address such issues. Rwanda, one of the EAC member countries, will be hosting the African Medicines Agency and with the combined efforts by the African Union Partners, with the support of the EAC work sharing initiative, will strengthen regulatory systems on the continent. The recommendations from this study included measuring and monitoring timelines, the availability of submission guidelines, the training and capacity building of regulatory reviewers as well as the publication of decision-making outcomes. If these recommendations are implemented, it is believed it will improve the effectiveness and efficiency of this regional initiative.

Poster presented at DIA Global 2023 conference, Boston, United States of America 25 to 27 June 2023 (See attachment)

Poster Presentation DIA Global 2023_Boston, USA June 2023



Abstracts for poster presentation at 6th Scientific Conference on Medical Products Regulation in Africa

6th Biennial Scientific Conference on Medical Products Regulation in Africa (SCoMRA VI)

THEME: Strengthening regulatory systems for the advancement of local production and increased access to medical products and technologies for Africans

5-7 December 2023

Cairo, Egypt

Abstract Submission Form

ABSTRACTS SUBMISSION FORM

Title of Abstract	**Evaluation of the Effectiveness and Efficiency of seven years' experience with the East African Community Joint Assessment**
Conference Sub-theme	**Theme 2: The future of Medical Products, Regulation, and Harmonization in the AMA era.**
Name and institutions of authors (1. is the Presenter; new rows may be created for new authors as necessary)	1. NANCY NGUM PROGRAMME OFFICER AUDA-NEPAD 2. Dr MARGARETH NDOMONDO-SIGONDA CONSULTANT 3. PROFESSOR SAM SALEK UNIVERSITY OF HERTFORDSHIRE
Abstract (minimum 250 and max 300 words)	**Objective:** Evaluating the effectiveness and efficiency of the current East African Community Medicines Regulatory Harmonization operating model, from both the regulators and applicants' perspective. **Method:** The Process Effectiveness and Efficiency Rating questionnaire was used to identify the benefits and challenges for improving the performance of the EAC initiative. This was completed by seven EAC Agencies and 14 pharmaceutical companies. **Results:** The East African Community Medicines Regulatory Harmonization regional initiative consists of seven agencies, namely Burundi, Kenya, Uganda, Rwanda, South Sudan, Tanzania, and Zanzibar. It has been of considerable value since it was established in 2009 as it moves towards achieving its main objectives of shorter timelines for approval of medicines, information sharing among regulators and capacity building for assessments, resulting in quicker access and increased availability of medicines for patients in the region. Pharmaceutical companies outlined how the initiative has facilitated the harmonisation of registration requirements across the EAC region leading to one registration for all countries and a reduction of the workload for both applicants and assessors. The key challenges identified by the agencies that have hindered the expected effectiveness and efficiency of this initiative were the lack of a centralised submission and tracking system; a lack of mandated registration; inadequate human resources, manufacturers' failure to submit the exact same dossier to all countries of interest; a lack of an integrated information management system and information on national medicines regulatory authority or EAC websites; and challenges in monitoring and tracking assessment reports. **Conclusion:**

Abstract for Student Poster for DIA Global 2024, San Diego, California, United States of America, 16-18 June 2024

Title Evaluation of Good Review Practices in member agencies of the East African Medicines Regulatory Harmonisation Initiative

Track 9: Regulatory or Track 10: Regulatory CMC and product quality

Key words East African Community work-sharing initiative, Good Review Practices, African Medicines Agency

Objective

To evaluate Good Review Practices (GReVP) in the agencies participating in the East African Medicine Regulatory Harmonisation Initiative and map strategies for moving forward as they are going through the process of alignment for the operationalisation of the African Medicines Agency (AMA).

Method

An established standardised questionnaire, the OpERA, which captures review processes was completed by the Head of the medicine's registration division in each of the seven NRAs. A country report based on the completed questionnaire for each NRA was validated by the heads of the respective agencies.

Results

The East African Community Medicines Regulatory Harmonization (EAC-MRH) regional initiative consists of seven agencies, namely Burundi, Kenya, Uganda, Rwanda, South Sudan, Tanzania and Zanzibar. A comparison of the quality measures recorded by the regulatory authorities indicated that Kenya, Rwanda and Tanzania implemented all eight quality measures while Uganda implemented 6, Zanzibar 4 and Burundi 5 out of eight. All five agencies use scientific expert committees. Only Uganda indicated that they did not have standard operating procedures and Burundi did not have assessment templates in place. All NRAs except Burundi are implementing a quality policy while except for Uganda and Zanzibar all four NRAs have a dedicated quality department. All six NRAs participated in shared and joint reviews. However, South Sudan did not implement any of the measures possibly because they are currently not reviewing any products.

On assessing the implementation of nine best practices on transparency and communication all six agencies reported that they have in place official guidelines to assist industry and a list of approved products that allow for industry to track the progress of their applications via email and telephone. Three agencies did not provide post-approval feedback to applicants on the quality of the submitted dossiers. Three agencies namely Kenya, Uganda and Tanzania reported that they do publish summary of assessment reports on which the approval was granted.

External and internal quality audits; internal tracking systems, reviews of assessors' and stakeholders' feedback, were assessed to determine continuous improvement initiatives. Tanzania and Zanzibar implemented all five initiatives, while Uganda and Kenya implemented four of the five initiatives. Rwanda implemented three and Burundi two out of five. All six

countries implemented measures on training and education and quality decision making practices.

Conclusion

Good Review Practices of agencies in the East African Medicine Regulatory Harmonisation Initiative could still be improved. This study has demonstrated how the EAC-MRH performs regulatory reviews in order to improve the capacity of NRAs.

For the AMA to be successful, country regulatory processes need to be streamlined and differences in country requirements minimised. Like the EAC-MRH, the AMA will also depend on countries to implement the decisions recommended by this continental body. It is therefore crucial that the operationalisation of the AMA focuses on improving the review practices of the NRAs to minimise any delay in granting marketing authorisation to medical products. It is imperative for countries to implement good review practices to accelerate patients' access to safe, quality and effective medical products when the AMA is fully operationalised.

Recommendations

Measuring & Monitoring Timelines. Agencies in the EAC-MRH initiative should implement systems that will enhance the measurement and monitoring of timelines for the key milestones of the registration process such as dates of submission, validation, start of scientific assessment, completion of scientific assessment and registration.

Applicants Communication: Clear registration processes should be documented and shared with the applicants as well as publishing timelines, assessment reports, and the summary basis of approval which will facilitate transparency and accountability.

Work-Sharing: The EAC-MRH should develop measures to mandate the registration of products at a national level following regional recommendation. This approach would ultimately lead to faster availability of medicines to patients as well as reducing demand on capacity.

Quality Decision-Making Practices: While the agencies indicated they are implementing quality decision making practices, there is still a need for further training and education to optimise decision making, meeting target timelines and patients' needs.

Appendix 3 : Questionnaire used to complete study 1 (Chapter 3) and Study 2 (Chapter 4)

Optimising ***E***fficiencies in ***R***egulatory ***A***gencies

QUESTIONNAIRE

[Country]

OpERA: Optimising Efficiencies in Regulatory Agencies

ASSESSING THE REGULATORY REVIEW PROCESS IN EMERGING MARKETS

Key milestones, target times, and quality of decision making in the assessment and registration process

Please return this questionnaire to:

Professor Stuart Walker Founder,
Centre for Innovation in Regulatory Science swalker@cirsci.org

Dr Neil McAuslane :
Scientific Director.
Centre for Innovation in Regulatory Science
nmcauslane@cirsci.org

CONTENTS

The Centre for Innovation in Regulatory Science (CIRS)

CIRS - The Centre for Innovation in Regulatory Science Limited - is a neutral, independently managed UK-based subsidiary company, forming part of Clarivate Analytics (UK) Limited. CIRS' mission is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and HTA policies and processes. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science and to facilitate access to medical products through these activities. This is CIRS' purpose. CIRS is operated solely for the promotion of its purpose.
The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities, special projects and grants.

Centre for Innovation in Regulatory Science (CIRS)
Friars House, 160 Blackfriars Road, London SE1 8EZ, United Kingdom Email:
cirs@cirsci.org
Website: www.cirsci.org

Confidentiality
CIRS recognises that much of these data may be highly sensitive. CIRS has more than 20 years of experience in handling similar data provided by agencies regarding individual products in regulatory review. **All information collected from individual agencies will be kept strictly confidential. No data that will identify an individual agency will be reported or made available to any third party.** External reports or presentations of the data will include only blinded results and any appropriate analytical interpretations.

ASSESSING THE REGULATORY REVIEW PROCESS IN EMERGING MARKETS

Review of key milestones, target times and quality of decision-making in the assessment and registration process

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BACKGROUND

This questionnaire supports an on-going programme by CIRS, focusing on the regulation of new medicines in emerging markets, and looking at how regulatory agencies build quality into their review process.

The first phase was initiated in January 2004 to assess the regulatory environment in some 30 countries, using comparative data, at the country and regional level, to identify the key issues for improving review practices and making new medicines available in an efficient and timely manner. Some of these, for example, the timing and use of the Certificate of a Pharmaceutical Product (CPP) and the length of the review process, were analysed in detail. This project highlighted the need to understand more about the different steps in the review process and the way in which these affect the overall timeline. Regulatory authorities also showed an interest in having a greater understanding of how agencies are building quality into the review process.

Through this on-going programme, CIRS maps the key milestones and associated activities, for each participating agency, for new marketing applications, and to identify the processes and procedures associated with the implementation of Good Review Practices (GRevP) that help build quality into the review process. This provides a platform to enable information sharing across agencies.

This questionnaire has been designed to collate information in a single place; agencies may have collected some of these data for other assessment (benchmarking) projects. However, **this project has several unique aspects**:

- It collects all the key information in a **single document** from which a consolidated Country Report will be created;
- It allows the metrics that are collected here and, in the future, to be related to the **PROCESS** that the agency uses thereby allowing for a more qualified assessment;
- It is part of a global programme called Optimising Efficiencies in Regulatory Agencies (OpERA), coordinated by CIRS on behalf of regulatory agencies around the world. The milestones and questions have been carefully crafted to be **relevant to any agency - large or small, mature or maturing - to provide relevant data that can be used for internal purposes or as applicable, for agency-to-agency comparisons**. For example, see Emel Mashaki Ceyhan et al: The Turkish Medicines and Medical Devices Agency: Comparison of Its Registration Process with Australia, Canada, Saudi Arabia, and Singapore. *Frontier's in Pharmacology* January 2018, Volume 9, Article 9.

OBJECTIVES

The objectives of this on-going programme are to:

- Identify the key milestones and target times for each agency and the main activities between milestones;
- Identify the model(s) of the review which is being undertaken by each agency;
- Identify opportunities for the exchange of better practices amongst regulatory authorities;
- Assess how agencies are building quality into the assessment and registration processes.

OUTPUT

Participating agencies will receive a Country Report derived from the data provided in this Questionnaire, with which they can compare their regulatory procedures with those of peer agencies across regions. This includes an analysis of where time is spent in the review process.

The outcome allows an analysis of the quality measures that are in place for a certain type of review, and provides a baseline for subsequent comparative studies across agencies to establish best practices.

ABOUT THE QUESTIONNAIRE

This questionnaire is divided into five sections:

Part 1: Organisation of the agency**:** The **Introduction** to the questionnaire asks the agency to provide current information on its structure, organisation and resources.

Part 2: Types of review models: Explores **review model(s)** for the **scientific assessment of medicines** in terms of the extent to which data is assessed in detail by the agency, and how the agency might rely on the results of assessments and reviews carried out elsewhere.

Part 3: Key milestones in the review process**s:** This part of the questionnaire is based on the General Model, giving a process map and milestones, that has been developed from studying procedures followed in 'established' and 'emerging' regulatory agencies. It captures the main steps in the review and approval process and identifies key 'milestone' dates in the process. This allows for the analysis of timelines.

Part 4: Good Review Practices (GRevP): Building quality into the regulatory process looks at the activities that contribute to those measures that have been adopted to improve consistency, transparency, timeliness, and competency in the review processes.

Part 5: Quality Decision-Making Processes**:** This part of the questionnaire explores to the quality of the decision-making process and whether the agency has measures in place to ensure that good decisions are made around the data during the registration process.

Where appropriate, additional information may be obtained during face-to-face agency-CIRS interactions.

FOCUS OF THE QUESTIONNAIRE

This questionnaire is intended, primarily, to document procedures and practices that relate to medicines that are the subject of **major** applications; i.e., new active substances and major line extensions (see Glossary).

New Active Substance (NAS)

A new chemical, biological, or pharmaceutical active substance including:

- a chemical, biological, or radiopharmaceutical substance not previously authorised as a medicinal product;
- an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance not previously authorised as a medicinal product, but differing in properties regarding safety and efficacy from that chemical substance previously authorised;
- a biological substance previously authorised as a medicinal product, but differing in molecular structure, nature of the source material or manufacturing process;
- a radiopharmaceutical substance which is radio nucleotide, or a ligand not previously authorised as a medicinal product, or the coupling mechanism to link the molecule and the radio nucleotide has not been previously authorised.

Major Line Extension (MLE)

A major line extension is a change to an authorised Medicinal Product that is sufficiently great that it cannot be considered as a simple variation to the original product, but requires a new product authorisation. Such changes include major new therapeutic indications or new disease states, extension to new patient populations (e.g., paediatrics), a new route of administration or a novel drug delivery system.

PART 1. ORGANISATION OF THE AGENCY

As background to the discussions about your agency, its practices and procedures it would be helpful to have the following basic information on its structure and the way it is organized:

Title of the Agency/Division responsible for the regulation of medicinal products for human use: ***Click or tap here to enter text.***

If this is part of a parent agency with a wider remit (e.g., food and drugs) please give the title: Click or tap here to enter text.

About the agency

1.1 Indicate which of the following best describes this agency:

☐ Autonomous agency, independent from the Health Ministry administration

☐ Operates within the administrative structure of the Health Ministry Date of establishment of the current agency: Click or tap here to enter text.

Scope of Activities

1.2 Please indicate the scope of responsibility of the agency:

☐ Medicinal products for human use
☐ Medicinal products for veterinary use
☐ Medical devices and in vitro diagnostics

1.3 Indicate the main activities that are covered by the agency:

☐ Marketing authorisations/product licences
☐ Clinical trial authorisations
☐ Post-marketing surveillance
☐ Regulation of advertising
☐ Laboratory analysis of samples
☐ Price regulation
☐ Other: Site inspections (site visits), Click or tap here to enter text.

Budget / Funding

Please indicate whether the following data:

☐ are in the public domain
☐ should be treated as confidential

1.4 Please provide the following information on the agency budget for the regulation of medicinal products for human use:

	Local currency (please specify: Click or tap here to enter text.)	**US$**
Total annual budget	Click or tap here to enter text.	Click or tap here to enter text.
Year for which data are given	Click or tap here to enter text.	
If the budget is sub-divided according to different activities, please specify % of total budget:		
Clinical trial authorisations	Click or tap here to enter text.	Click or tap here to enter text.
Marketing authorisations	Click or tap here to enter text.	Click or tap here to enter text.
Pharmacovigilance	Click or tap here to enter text.	Click or tap here to enter text.
Other post-marketing controls	Click or tap here to enter text.	Click or tap here to enter text.
Other activities, please specify: *Click or tap here to enter text.*	Click or tap here to enter text.	Click or tap here to enter text.

Sources of funding

1.5 Please provide the following information in relation to the way the agency is funded:

☐ Funded entirely by the government
☐ Self-funded entirely from fees
☐ Partially funded from different sources (please give proportions of total budget):

% Government: Click or tap here to enter text.
% Fees: Click or tap here to enter text.
% Other (please specify): Click or tap here to enter text.

Review team

Please note that the following questions refer to the regulation of **medicinal products for human use.**

1.6 Please provide information on staff numbers:

- Total staff in the agency: Click or tap here to enter text.
- Total number of reviewers for applications for marketing authorisations/ product licences: Click or tap here to enter text.
- Number of reviewers for applications for marketing authorisations/ product licences or synthetic and biological products: Click or tap here to enter text.

1.7 Please indicate the professional background and numbers of the technical agency staff assigned to the review and assessment of medicinal products:

	Number employed as assessors (degree/expertise)			
	Total	with PhD or PharmD	with Master Degree	Other
Physicians	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
Statisticians	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
Pharmacists	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
Other Scientists	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
Project Managers	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.

Fees charged for review applications

1.8 Are fees charged to sponsors for the review and assessment of applications for medicinal products for human use?

☐ YES
☐ NO

*1.9 If **YES**, please provide the following information:*

Marketing Authorisation Application fee for:	**Local currency (please specify:** Click or tap here to enter text.**)**	**US$ (rounded)**
New Active Substance synthesis	Click or tap here to enter text.	Click or tap here to enter text.
New Active Substance biological	Click or tap here to enter text.	Click or tap here to enter text.
Established ingredient - proprietary product synthesis	Click or tap here to enter text.	Click or tap here to enter text.
Established ingredient - proprietary product biological	Click or tap here to enter text.	Click or tap here to enter text.
Generic product	Click or tap here to enter text.	Click or tap here to enter text.
Biological competitor product	Click or tap here to enter text.	Click or tap here to enter text.
Variations	Click or tap here to enter text.	Click or tap here to enter text.
Major line extension	Click or tap here to enter text.	Click or tap here to enter text.
Other (Please specify)	Click or tap here to enter text.	Click or tap here to enter text.
Does the agency charge a fee for scientific advice? ☐ YES ☐ NO If **YES,** please provide fee ➔	Click or tap here to enter text.	Click or tap here to enter text.

Applications

1.10 Applications received

Type	Number of applications received in each year			Current backlog
	2019	2020	2021	
New Active Substances	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
Major line extensions	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
Generics (all)	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
WHO Pre-qualified generics (if applicable)	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.

1.11 Applications determined

Type	Number of applications determined in each year		
	2019	2020	2021
New Active Substances approved	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
New Active Substances refused	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
Major line extensions approved	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
Major line extension refused	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
Generics approved	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
Generics refused	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
WHO Pre-qualified generics approved	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
WHO Pre-qualified generics refused	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.

Additional documentation

To assist CIRS to better understand your organisation, please provide copies of any** organisation charts **that show the structure of the agency and its relationship to other regulatory bodies; e.g., medical device agency. It would also be very useful to have copies of any background papers that describe the** functions, remit, **and** mission **of the

PART 2. TYPES OF REVIEW MODELS

Three basic types of scientific review have been identified. Many agencies apply a different level of data assessment to different applications, according to the type of product and/or its regulatory status with other agencies. The data assessment models for scientific review are described below and further questions are set out to analyse the types of scientific review in more detail.

Please indicate by checking the boxes below, which descriptions fit the model(s) used by your agency in the assessment of major applications i.e., new active substances (NASs) and major line extensions (MLE) as described earlier.

Data Assessment Type 1 (Verification)

This model is used to reduce duplication of effort by agreeing that the importing country will allow certain products to be marketed locally once they have been authorised by one or more recognised reference agencies, elsewhere. The main responsibility of the agency in the importing country is to 'verify' that the product intended for local sale has been duly registered as declared in the application and that the product characteristics (formulation, composition) and the prescribing information (use, dosage, precautions) for local marketing conforms to that agreed in the reference authorisation(s).

2.1 Type 1 is:

☐ Not used
☐ Used for all major applications
☐ Used for selected applications (please specify): Click or tap here to enter text.

Comment: Click or tap here to enter text.

2.2 Data requirements for Type 1 Assessments (verification) - What do you review/assess?

CPP/Public assessment reports/un-redacted assessment reports/Free sales certificate/etc	Click or tap here to enter text.
Similarity to registered product	Click or tap here to enter text.
Quality data	Click or tap here to enter text.
Non-clinical data	Click or tap here to enter text.
Clinical data	Click or tap here to enter text.
Local benefit-risk assessment	Click or tap here to enter text.

Data Assessment Type 2 (Abridged)

This model also conserves resources by not re-assessing scientific supporting data that has been reviewed and accepted elsewhere but includes an 'abridged' independent review of the product in terms of its use under local conditions. This might include a review of the pharmaceutical (CMC) data in relation to climatic conditions and distribution infrastructure and a benefit-risk assessment in relation to use in the local ethnic population, medical practice/culture and patterns of disease and nutrition.

Approval by a recognised agency elsewhere is a pre-requisite before the local authorisation can be granted but the initial application need not necessarily be delayed until formal documentation such as a Certificate of a Pharmaceutical Product (CPP) is available.

2.3 Type 2 is:

☐ Not used
☐ Used for all major applications
☐ Used for selected applications (please specify): Click or tap here to enter text.

Comment: Click or tap here to enter text.

2.4 Data requirements for Type 2 Assessments (abridged)- What do you review/assess?

CPP/Public assessment reports/un-redacted assessment reports/Free sales certificate/etc	Click or tap here to enter text.
Similarity to registered product	Click or tap here to enter text.
Quality data	Click or tap here to enter text.
Non-clinical data	Click or tap here to enter text.
Clinical data	Click or tap here to enter text.
Local benefit-risk assessment	Click or tap here to enter text.

Data Assessment Type 3 (Full)

In this model the agency has suitable resources, including access to appropriate internal and external experts, to carry out a 'full' review and evaluation of the supporting scientific data (quality, pre-clinical, clinical) for a major application. A Type 3 assessment could be carried out on a new application that has not been approved elsewhere but, in practice, legal requirements may dictate that the product must be authorised by a reference agency before the local authorisation can be finalised.

2.5 Type 3 is:

☐ Not used
☐ Used for all major applications
☐ Used for selected applications (please specify): Click or tap here to enter text.
☐ Full review conducted but product must still be authorised by a reference agency prior to final authorisation

Comment: Click or tap here to enter text.

2.6 Data requirements for Type 3 Assessments (full)- What do you review/assess?

CPP/Public assessment reports/un-redacted assessment reports/Free sales certificate/etc	Click or tap here to enter text.
Similarity to registered product	Click or tap here to enter text.
Quality data	Click or tap here to enter text.
Non-clinical data	Click or tap here to enter text.
Clinical data	Click or tap here to enter text.
Local benefit-risk assessment	Click or tap here to enter text.

Recognized reference agencies

*2.7 If your agency has **recognised 'reference agencies'** (as may be used for reliance or recognition in Types 1 and 2 reviews) please list the countries/agencies/authorities:*

Click or tap here to enter text.

Priority / fast-track products

2.8 Does your company have available:

☐ A priority review track
☐ A fast track (if different from priority)

Data requirements and assessment

2.9 Please tick relevant boxes in the following table

		Type 1		Type 2		Type 3	Priority/fast track products
Evidence of authorisation by other authorities	Requirements for a CPP as part of the review	☐ with application ☐ before authorisation ☐ not essential		☐ with application ☐ before authorisation ☐ not essential		☐ with application and before local authorisation ☐ not essential ☐ if available at the time of submission	☐ with application ☐ before authorisation ☐ not essential
	Other documentation from the authorising agencies accepted as evidence of registration	☐ letter of authorisation ☐ copy of full authorisation ☐ Internet evidence		☐ letter of authorisation ☐ copy of full authorisation ☐ Internet evidence		letter of authorisation copy of full authorisation ☐ Internet evidence ☐ None	letter of authorisation copy of full authorisation ☐ Internet evidence ☐ None
	Other evidence accepted	Click or tap here to enter text.		Click or tap here to enter text.		Click or tap here to enter text.	Click or tap here to enter text.
Verification of identity between the authorised product and the local application		**Type 1**		**Type 2**		**Type 3**	
	Information must be:	*Identical*	*Closely similar*	*Identical*	*Closely similar*	*Not applicable*	
	Dosage form	☐	☐	☐	☐		
	Strength	☐	☐	☐	☐		
	Ingredients	☐	☐	☐	☐		
	Indications and dosage	☐	☐	☐	☐		
	Warnings and precaution	☐	☐	☐	☐		
	Product label	☐	☐	☐	☐		
	Product name	☐	☐	☐	☐		
	Other (specify)	☐	☐	☐	☐		
Scientific data required to		**Type 1**		**Type 2**		**Type 3**	**Priority/fast track products**

support the application (Reference is made below to sections of the ICH Common Technical Document (CTD) as an example of the level of detail but does not imply that the CTD in necessarily accepted	Pharmaceutical quality/CMC	Summary data (Mod 2.3) Summary + full stability ☐ Full data (Mod 3)	Summary data (Mod 2.3) ☐ Summary + full stability ☐ Full data (Mod 3)	☐ Summary data (Mod 2.3) ☐ Summary + full stability ☐ Full data (Mod 3)	☐ Summary data (Mod 2.3) ☐ Summary + full stability ☐ Full data (Mod 3)
	Non-clinical data	☐ Written summary (Mod 2.4) ☐ Tabulated data (Mod 2.5) ☐ Full data (Mod 4)	☐ Written summary (Mod 2.4) ☐ Tabulated data (Mod 2.5) ☐ Full data (Mod 4)	☐ Written summary (Mod 2.4) ☐ Tabulated data (Mod 2.5) ☐ Full data (Mod 4)	☐ Written summary (Mod 2.4) ☐ Tabulated data (Mod 2.5) ☐ Full data (Mod 4)
	Clinical data	☐ Written summary (Mod 2.5) ☐ Tabulated data (Mod 2.6) ☐ Full data (Mod 5)	☐ Written summary (Mod 2.5) ☐ Tabulated data (Mod 2.6) ☐ Full data (Mod 5)	☐ Written summary (Mod 2.5) ☐ Tabulated data (Mod 2.6) ☐ Full data (Mod 5)	☐ Written summary (Mod 2.5) ☐ Tabulated data (Mod 2.6) ☐ Full data (Mod 5)
Extent of Scientific Review		**Type 1**	**Type 2**	**Type 3**	**Priority/fast track products**
	Quality/CMC data	☐ Only examined if there is a query ☐ 'Check list' review for completeness of data ☐ Selective review in detail (e.g. stability, specification) ☐ Detailed assessment and evaluation report	☐ Only examined if there is a query ☐ 'Check list' review for completeness of data ☐ Selective review in detail (e.g. stability, specification) ☐ Detailed assessment and evaluation report	☐ Only examined if there is a query ☐ 'Check list' review for completeness of data ☐ Selective review in detail (e.g. stability, specification) ☐ Detailed assessment and evaluation report	☐ Only examined if there is a query ☐ 'Check list' review for completeness of data ☐ Selective review in detail (e.g. stability, specification) ☐ Detailed assessment and evaluation report
	Comments:	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
	Non-clinical data	☐ Only examined if there is a query ☐ 'Check list' review for completeness of data ☐ Detailed assessment and evaluation report	☐ Only examined if there is a query ☐ 'Check list' review for completeness of data ☐ Detailed assessment and evaluation report	☐ Only examined if there is a query ☐ 'Check list' review for completeness of data ☐ Detailed assessment and evaluation report ☐ Not at all	☐ Only examined if there is a query ☐ 'Check list' review for completeness of data ☐ Detailed assessment and evaluation report

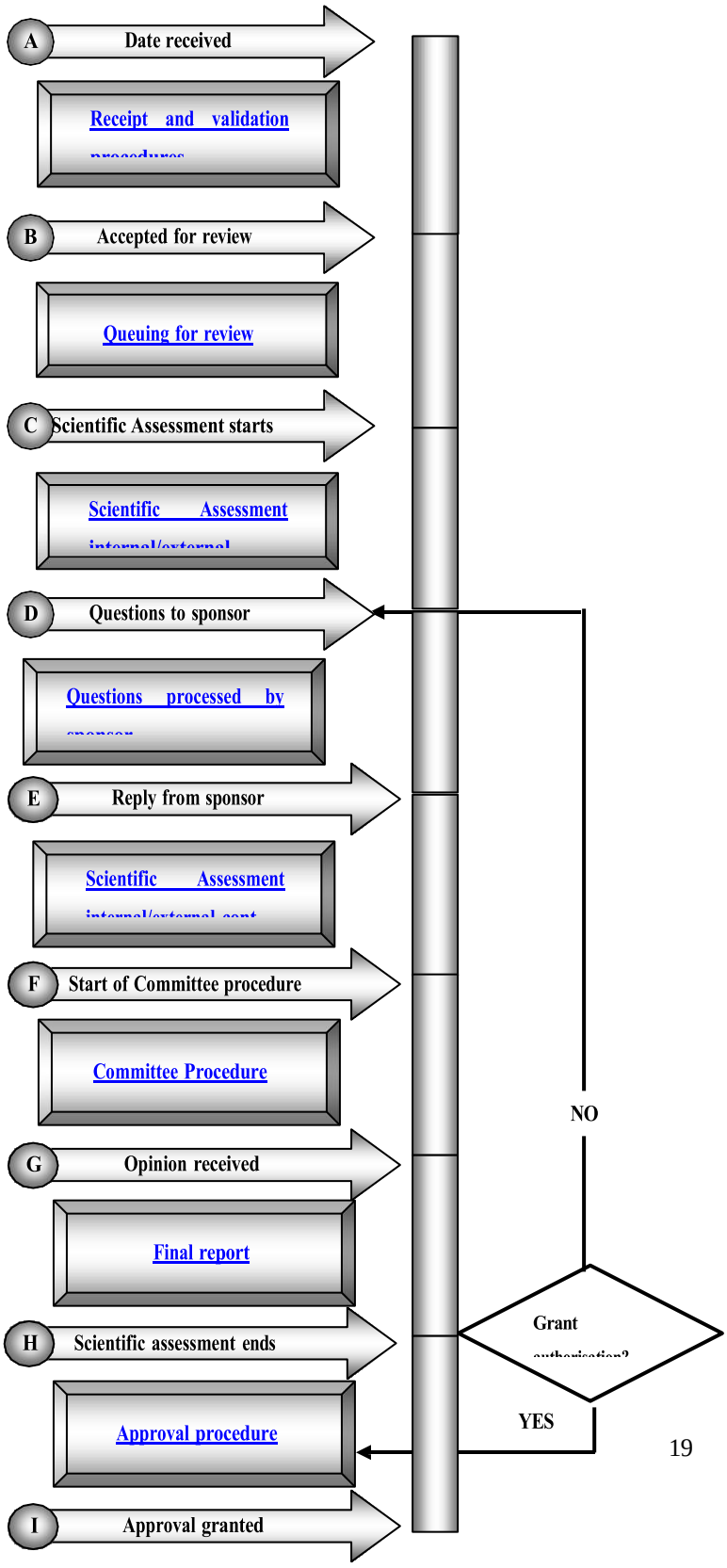
	Comments:	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
	Clinical data	☐ Only examined if there is a query ☐ 'Check list' review for completeness of data ☐ Selective review in detail (e.g. stability, specification) ☐ Detailed assessment and evaluation report	☐ Only examined if there is a query ☐ 'Check list' review for completeness of data ☐ Selective review in detail (e.g. stability, specification) ☐ Detailed assessment and evaluation report	☐ Only examined if there is a query ☐ 'Check list' review for completeness of data ☐ Selective review in detail (e.g. stability, specification) ☐ Detailed assessment and evaluation report	☐ Only examined if there is a query ☐ 'Check list' review for completeness of data ☐ Selective review in detail (e.g. stability, specification) ☐ Detailed assessment and evaluation report
	Comments:	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
Clinical evaluation: factors included in the risk-benefit assessment	*The clinical opinion takes account of:*	**Type 1**	**Type 2**	**Type 3**	**Priority/fast track products**
	Differences in medical culture/practice	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always
	Ethnic factors	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always
	National disease patterns	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always
	Unmet medical need	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always
Additional information, not in the application	*The agency tries to obtain:*	**Type 1**	**Type 2**	**Type 3**	**Priority/fast track products**
	Other agencies' internal assessment reports	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always
	Reports available on the Internet (e.g., EPARS)	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always

	General Internet search	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always
	Other data (please specify): Click or tap here to enter text.	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always	☐ Never ☐ Sometimes ☐ Always

PART 3. KEY MILESTONES IN THE REVIEW PROCESS

Review Process Map and Milestones

This part of the questionnaire is based on the **General Model** below, giving a process map and milestones that have been developed from studying procedures followed in 'established' and 'emerging' regulatory agencies. It captures the main steps in the review and approval process and identifies key 'milestone' dates in the process for monitoring and analysing timelines.



Notes

Receipt and validation may include administrative registration (reference number) and checks on legal requirements, status of company, local agent, manufacturer etc. as well as a 'checklist' validation of the application content (e.g., technical sections, CPP status).

Queuing for review: *Administrative time 1* is a measure of the 'backlog' time (if any) while valid applications wait for action to begin.

Scientific Assessment extends from milestone C to milestone H and is a measure of 'review time.' In some systems, the 'clock' stops when questions are asked and Sponsor ***time*** (milestone D to milestone E) can be measured and deducted from the agency review time.

Questions to sponsor may be batched and sent at one time or asked throughout the review process, in which case the *Sponsor time* is not easily measured.

In some systems, questions may only be sent to the sponsor after the end of the 'first cycle' scientific assessment (at milestone H).

Committee Procedure: Most review procedures for major applications include a step where the opinion of an expert advisory committee is sought. In this scheme, the Committee procedure is 'nested' within the Scientific Assessment but it may take place after the Agency's scientific assessment is complete.

Second cycle: If the application cannot be granted immediately, on technical grounds, it enters a second review cycle (new data point D: questions to sponsor) and a further scientific assessment is made of the additional data. The Committee Procedure may or may not need to be included in the second and subsequent review cycles.

Approval procedure: The time interval after scientific review (*Admin time 2*) while the formal authorisation is issued may be extended by pricing negotiations and finalisation of analytical and GMP checks.

Approval time is measured from milestone A to milestone I.

Review stages and milestones

This section of the questionnaire is based on the ***General Model***.

We recognise that not all systems conform to the ***General Model*** and it would be very helpful if you could provide an outline of the model used by your agency. If this differs according to the **Type of data assessment** (see Part 2. Types of Review Models) please provide information on the different models.

3.1 When information is given on target or actual times please indicate here whether these are counted in:

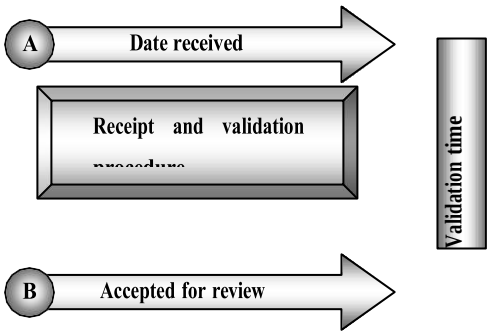
☐ Calendar days
☐ Working days

3.2 When 'milestone' dates are recorded during the review process is the information entered into an electronic tracking/recording system?

☐ YES, a system is in current use
☐ NO, a system is in development (please specify target date): Click or tap here to enter text.
☐ NO, a manual system will be used for the foreseeable future

3.3 Receipt and Validation

Pre-submission requirements



3.3.1 Are there any formal requirements before an application is submitted, for example, notification of intent to submit, assignment of registration code etc.?

☐ No
☐ YES (please specify): Click or tap here to enter text.

Validation

3.3.2 Is the date of receipt (milestone A) formally recorded?

☐ YES ☐ NO

3.3.3 Are the following administrative items checked in the pre-review validation process?

- Legal status of applicant/local agent: ☐ YES ☐ NO
- GMP status of manufacturer: ☐ YES ☐ NO

- Patent/IP status of active ingredient: ☐ YES ☐ NO

- Whether company has paid the correct fee: ☐ YES ☐ NO
- Other: Click or tap here to enter text.

For those applications where prior authorisation elsewhere is essential (see Part 2 – Types of Review Models) please answer the following questions about the Certificate of a Pharmaceutical Product (CPP):

3.3.4 Is the inclusion of a CPP an absolute requirement before accepting the application as valid?

☐ Yes

☐ NO

☐ For some applications (please specify): Click or tap here to enter text.

*3.3.5 **If YES**, must the CPP be legalised by an Embassy or Consulate?*

☐ Yes

☐ NO

*3.3.6 **If NO**, please indicate which of the following apply:*

- A CPP must be provided before the authorisation is issued: ☐ YES ☐ NO
- Other evidence of authorisation by other countries is accepted in place of the CPP (e.g., copy of authorisation, Internet reference): ☐ YES ☐ NO

Comments: Click or tap here to enter text.

3.3.7 Is the application also checked for the following items?

- Acceptable format (e.g. ICH CTD or local requirements): ☐ YES ☐ NO
- Correct sections of scientific data (quality, safety, efficacy): ☐ YES ☐ NO
- Other technical items: Click or tap here to enter text.

Acceptance for review/refusal to file

3.3.8 Is the date of acceptance (milestone B) formally recorded?

☐ YES ☐ NO

3.3.9 What happens if the application is incomplete?

☐ Refusal to file: New application must be made

☐ File pending: A request for the missing data is sent to the applicant

*3.3.10 In case of **file pending**, what is the time limit for the applicant to reply?*

Click or tap here to enter text.

Comments: Click or tap here to enter text.

Target time for validation

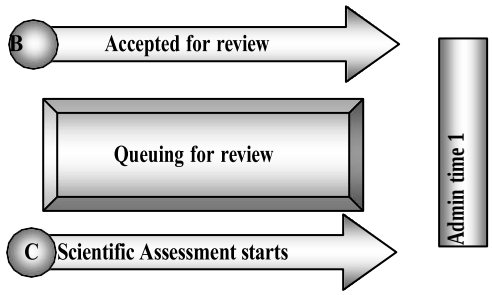
3.3.11 Is there a target validation time?

☐ YES ☐ NO

*3.3.12 If **YES**, please specify:*

Click or tap here to enter text.

3.4 Queuing/backlog



3.4.1 Which of the following applies to the queuing system for new applications?

☐ Held in queue after validation (as in the General Model) after phase 1 validation
☐ Held in queue before validation starts (milestone A)

3.4.2 What is the current queue time (approximately)?

☐ Less than 2 weeks
☐ 2-8 weeks
☐ 2-6 months
☐ 6 months-1 year
☐ More than 1 year

3.4.3 Are priority products taken out of turn in the queuing system?

☐ YES, always
☐ YES, sometimes
☐ NO, all applications await their turn

Comments: Click or tap here to enter text.

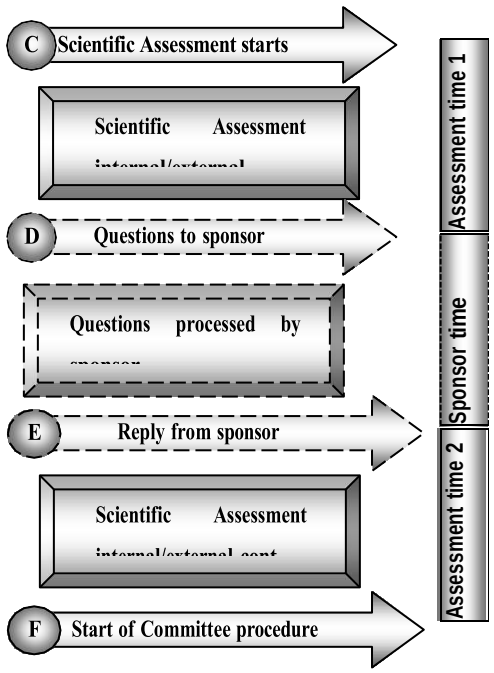
3.4.4 Does the agency regard the backlog of applications as a problem?

☐ YES ☐ NO

*3.4.5 If **YES**, how is this being addressed:*

Click or tap here to enter text.

3.5 Scientific Assessment



Initiation of scientific review

3.5.1 Is the start of the Scientific Assessment formally recorded (milestone C)?

☐ YES ☐ NO

3.5.2 Is the scientific data separated into three sections (quality, safety, and efficacy) for review?

☐ YES ☐ NO

3.5.3 In what order are the different sections assessed?

☐ In parallel ☐ In sequence

*3.5.4 If **in sequence**, please give order:*

Click or tap here to enter text.

3.5.5 Who carries out the primary scientific assessment?

☐ Agency technical staff
☐ Sent to outside experts
☐ Different procedure for different sections

Please describe the process: Click or tap here to enter text.

Use of outside experts

If outside experts are used for the assessment of scientific data (Milestone C above) please complete the following:

3.5.6 Number of experts on the agency's list or panel:

Click or tap here to enter text.

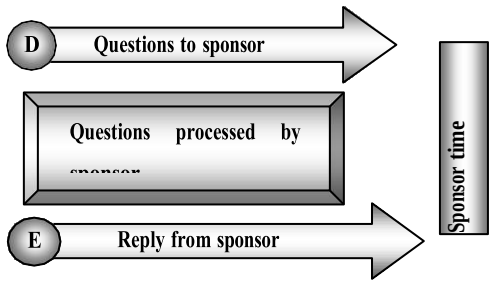
3.5.7 Main responsibility:

☐ To provide a detailed assessment report and recommendation
☐ To provide a clinical opinion on the product
☐ To provide advice to the agency staff on specific technical issues
☐ Other (Please specify): Click or tap here to enter text.

3.5.8 Is there a contractual agreement on working within deadlines set by the agency?

☐ YES ☐ NO

3.6 Interactions with the Sponsor



3.6.1 How are questions sent to the Sponsor?

☐ As they arise during the assessment
☐ Collected into a single batch

3.6.2 When are batched questions sent to the Sponsor?

☐ After the initial assessment but before reporting to the Scientific Committee (as in the General model)
☐ Not until the Scientific Committee has given its advice
☐ Before and after reference to the Scientific Committee

3.6.3 Does the scientific review cease while questions are being processed by the Sponsor ('clock stop')?

☐ YES ☐ NO

3.6.4 Can the sponsor time be calculated, i.e., are milestones D and E recorded?

☐ YES ☐ NO

3.6.5 Is the sponsor given a time limit to reply?

☐ YES ☐ NO

3.6.6 If Yes, what time is allowed?

Click or tap here to enter text.

Meetings

3.6.7 Can the Sponsor hold meetings with the agency staff to discuss questions and queries that arise during the assessment?

☐ YES ☐ NO

*3.6.8 If **Yes**, what conditions and restrictions (if any) are applied:*

Click or tap here to enter text.

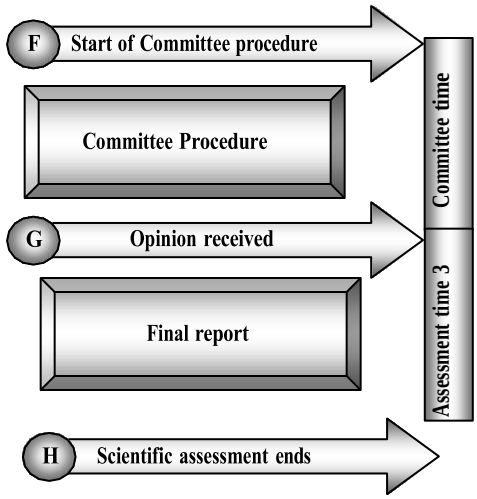
3.6.9 Can the Sponsor hold meetings with the agency staff to discuss questions and queries that arise during the assessment?

☐ YES ☐ NO

*3.6.10 **If Yes**, what conditions and restrictions (if any) are applied:*

Click or tap here to enter text.

3.7 Review by Scientific Committee(s)



3.7.1 Is a Committee of Experts (internal and/or external) used in the review process?

☐ YES ☐ NO

3.7.2 If YES, at which stage in the review?

☐ Responsible for the whole assessment of the dossier from the start of the review
☐ Integrated into the agency's own internal/external scientific review procedure
☐ Consulted after the agency has reviewed and reported on the scientific data
☐ Other (Please specify): Click or tap here to enter text.

3.7.3 Are the dates at the start and end of the Committee Review recorded (milestones F and G)?

☐ YES ☐ NO

3.7.4 Is the agency mandated to follow the Committee recommendation?

☐ YES ☐ NO

3.7.5 Is there a time limit for the Committee Procedure?

☐ YES ☐ NO

*3.7.6 **If YES**, please give the target:*

Click or tap here to enter text.

*3.7.7 **If NO**, what is the time range?*

Click or tap here to enter text.

3.7.8 Is there an additional step in the scientific review process, after the Committee has given its opinion?

☐ YES ☐ NO

3.7.9 If YES, please describe briefly the work carried out at this stage (e.g., final report and agency opinion):

Click or tap here to enter text.

3.7.10 If NO, the milestone G will mark the end of the scientific review for the purpose of calculating the review time:

Click or tap here to enter text.

Target timelines for the review process

3.7.11 Is a target time set for the scientific review (milestones C to H)?

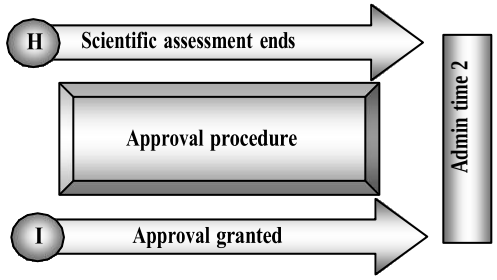
☐ YES ☐ NO

*3.7.12 If **YES** please give target*

Click or tap here to enter text.

3.8 Recommendation on the Application

At the end of the Scientific Review (see General Model) there is normally recommendation that either:



- The product meets the scientific criteria for authorisation (proceed to approval procedure) *or*
- Further data is required before the scientific criteria are met (application enters a **second cycle** at milestone D (questions to Sponsor) *or*
- The application should be refused (not shown in the General Model)

Responsibility for the authorisation decision

3.8.1 Who makes the decision that a marketing authorisation can be granted?

☐ The Scientific Advice Committee
☐ The Head of the Agency
☐ The Minister of Health
☐ Other (please specify): Click or tap here to enter text.

3.8.2 If Scientific Advice Committee is used as per 3.8.1, what kind of decision-making process is used?

☐ Consensus process by the Committee
☐ Majority vote by the Committee
☐ One individual makes the final decision based on the Committee recommendations
☐ Other (please specify): Click or tap here to enter text.

Other criteria to be met

*3.8.3 Is the issue of the authorisation dependent on a **pricing agreement**?*

☐ YES ☐ NO

*3.8.4 **If YES**, when are the pricing negotiations started?*

☐ At the start of the scientific review
☐ After the end of the scientific review
☐ After the start but before the end of the scientific review

*3.8.5 Is the issue of the authorisation dependent on **sample analysis**?*

☐ YES ☐ NO

*3.8.6 **If YES**, when is the analytical work started?*

☐ In parallel with the scientific review
☐ At the end of the scientific review
☐ After the start, but before the end of the scientific review

*3.8.7 Is there a separate **negotiation of the product labelling/product information** after the scientific opinion is given but before the approval is issued?*

☐ YES ☐ NO

Comments: Click or tap here to enter text.

3.8.8 Please specify any other legal/administrative matters that must be finalised before the approval can be issued:

Click or tap here to enter text.

3.8.9 Is the sponsor informed of a positive scientific opinion at milestone G, i.e., before the authorisation is issued?

☐ YES ☐ NO

3.8.10 Approximately how long does it take from receiving a positive scientific opinion (at milestone H) to issuing an approval (milestone I)?

☐ Less than a month
☐ 1-3 months
☐ 3-6 months
☐ Over 6 months

Comments: Click or tap here to enter text.

3.9 Metrics on the Approval Process

It would be very helpful to have the following information on processing times for marketing authorisations that have been received and/or determined in the three years:

3.9.1 Actual approval times (average)

Type	Time from receipt of application to issue of approval		
	2019	2020	2021
New Active Substances approved Full Review Abridged Review Verification Review	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
Major Line Extensions approved Full Review Abridged Review Verification Review	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
Generics approved Full Review Abridged Review Verification Review	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
WHO Pre-qualified generics approved Review Model?	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.

PART 4. GOOD REVIEW PRACTICES (GRevP): BUILDING QUALITY INTO THE REVIEW PROCESS

Quality in the assessment and registration process is important to regulatory authorities as it ensures consistency, transparency, timeliness and competency in the review processes. Regulatory authorities are continuously developing and implementing a variety of measures to improve and achieve higher quality standards and to meet the expectations of industry and the general public. The purpose of this section of the questionnaire is to obtain an insight into the strategies, measures and resources that agencies have in place to develop and maintain quality in their review processes.

4.1 General measures used to achieve quality

Please indicate the quality measures currently in place and, where there are none, what, if any, plans there are to introduce such measures in the foreseeable future.

Good Review Practices (GRevP)

"*A code about the process and the documentation of review procedures that aims to standardise and improve the overall documentation and ensure timeliness, predictability, consistency and high quality of reviews and review reports"* (see Glossary).

4.1.1 How does your agency define GRevP: Is it different from the Glossary?

☐ YES ☐ NO

4.1.2. ***If different****, please define here:*

Click or tap here to enter text.

4.1.3 Please outline the key elements that make up GRevP in your agency:

Click or tap here to enter text.

4.1.4 Has the agency formally or informally implemented GRevP?

☐ YES (Formally)
☐ YES (Informally)
☐ NO

4.1.5 ***If YES****, please give the title and date of formal implementation:*

Click or tap here to enter text.

4.1.6 How has this been implemented? (Please select the appropriate box(s)):

☐ Guidelines
☐ Standard Operating Procedure (SOP)
☐ GRevP Training Program
☐ Other (Please specify): Click or tap here to enter text.

4.1.7 Are these documents open and available to the public?

☐ YES ☐ NO

4.1.8 ***If YES****, please describe how:*

Click or tap here to enter text.

4.1.9 Are these documents open and available to the public?

☐ YES ☐ NO

4.1.10 ***If YES****, please describe how:*

Click or tap here to enter text.

4.1.11 Was the establishment of your GRevP based on other agencies or International standards?

☐ YES ☐ NO

4.1.12 ***If YES,*** *please state the name of the agency(ies)/ or internationals standards on which your GRevP has been based:*

Click or tap here to enter text.

4.1.13 Are you satisfied with your existing GRevP framework?

☐ Satisfied
☐ Could be improved
☐ Unsatisfied

4.1.14 ***If could be improved or unsatisfied****, please select the reason(s) that best describes your situation:*

☐ System still evolving
☐ Requires additional training to understand and learn about Good Review Practice
☐ Poor acceptance/utilization by staff
☐ Benefits of implementing GRevP are not apparent so far
☐ Other (please provide details): Click or tap here to enter text.

4.1.15 If you do not have a formal GRevP system in place are there plans to establish this within the next two years?

☐ YES ☐ NO

Internal Quality Policy

"*Overall intentions and direction of an organisation related to quality as formally expressed by top management*" (see Glossary).

4.1.16 Does the agency have an Internal Quality Policy?

☐ YES ☐ NO

4.1.17 ***If NO****, are there plans to establish this within the next two years?*

☐ YES ☐ NO

SOPs

"*SOPs (Standard Operating Procedures) are written documents that describe in detail the routine procedures to be followed for a specific operation*" (see Glossary).

4.1.18 Are there SOPs for the guidance of scientific assessors?

☐ YES ☐ NO

4.1.19 ***If NO****, are there plans to establish SOPs within the next two years?*

☐ YES ☐ NO

4.1.20 Are there SOPs for the advisory committee consulted during the review process?

☐ YES
☐ NO
☐ No committee

4.1.21 ***If NO****, are there plans to establish SOPs within the next two years?*

☐ YES ☐ NO

4.1.22 Are SOPs used for any other procedures in the regulatory review process (e.g., validation)?

☐ YES, please specify: Click or tap here to enter text.
☐ NO

Assessment Templates

"set out the content and format of written reports on scientific reviews" (see Glossary).

4.1.23 Are there Assessment Templates for reports on the scientific review of an NAS?

☐ YES ☐ NO

4.1.24 ***If NO****, are there plans to establish this within the next two years?*

☐ YES ☐ NO

4.1.25 ***If YES****, are these based on another agency's assessment template?*

☐ YES, please specify which agency(ies): Click or tap here to enter text.

☐ NO

4.1.26 Is there an SOP for completing an assessment template?

☐ YES ☐ NO

4.1.27 Select which elements from the list below are included in your agency assessment template:

☐ Drug Substance
☐ Drug Product
☐ Comments on label
☐ Non-clinical GLP Aspects
☐ Non-clinical Pharmacokinetic
☐ Toxicology
☐ Regulatory background (worldwide status on regulatory agencies)
☐ GCP aspects
☐ Clinical Pharmacology (PK & PD)
☐ Clinical Efficacy
☐ Clinical Safety
☐ List of questions for sponsors
☐ Benefit Risk Reduction
☐ Ethnic factors (e.g., consideration of bridging studies)
☐ Other (please specify): Click or tap here to enter text.

4.1.28 Would the agency be open to sharing their assessment template or points to consider with CIRS?

☐ YES ☐ NO

Assessment report

4.1.29 Do you produce an assessment report (AR) following the review?

☐ YES ☐ NO

*4.1.30 **If YES**, is there an SOP for completing the AR?*

☐ YES ☐ NO

4.1.31 What language is the AR prepared in?

☐ Local language
☐ English

4.1.32 Do you share your AR with other regulatory authorities?

☐ YES
☐ NO
☐ Sometimes

*4.1.33 Do you put your **full** AR on the website?*

☐ YES
☐ NO
☐ Sometimes

*4.1.34 Do you put your **abridged** AR on the website?*

☐ YES
☐ NO
☐ Sometimes

*4.1.35 Do sponsors get a copy of the **full** assessment report?*

☐ YES ☐ NO

4.1.36 Do sponsors have any involvement in the following in relation to AR:

☐ Preparation of assessment reports
☐ Comments on the assessment reports
☐ Translation of assessment reports
☐ Distribution of assessment reports

Peer Review

"*is an additional evaluation of an original assessment that is carried out by an independent person or committee. Peer review can occur either during assessment of a dossier or at the time of sign-off*" (see Glossary).

*4.1.37 Are **external** peer reviews carried out when a NAS is assessed?*

☐ YES ☐ NO

*4.1.38 **If NO**, are there plans to introduce these within the next two years?*

☐ YES ☐ NO

*4.1.39 Are **internal** peer reviews carried out when a NAS is assessed?*

☐ YES ☐ NO

*4.1.40 **If NO**, are there plans to introduce these within the next two years?*

☐ YES ☐ NO

4.1.41 Are there other general procedures in place to monitor the quality of the review process?

☐ YES ☐ NO

4.1.42 What other tools does your agency use to build quality into the assessment process? (e.g., Internal procedure could include: quality assurance and quality control meeting; stakeholder meeting; channel for grievance; survey of performance from sponsors)

Click or tap here to enter text.

4.2 Quality Management

Reasons for introducing quality measures in the agency

4.2.1 From the following list, please select the three most important reasons for the introduction of quality measures:

☐ To be more efficient
☐ To ensure consistency
☐ To achieve stakeholder satisfaction

☐ To improve predictability
☐ To minimise errors
☐ To increase transparency
☐ To improve communications in the agency
☐ To allocate the regulatory resources
☐ Other (please specify): Click or tap here to enter text.

Monitoring to improve quality

4.2.2 Which of the following activities are undertaken by the agency to bring about continuous improvement in the assessment and registration process?

☐ Reviewing assessors' feedback and taking necessary action
☐ Reviewing stakeholders' feedback (e.g. through complaints, meetings or workshops) and taking necessary action
☐ Using an internal tracking system to monitor (e.g. consistency, timeliness, efficiency and accuracy)
☐ Carrying out internal quality audits (e.g. self-assessments) and using findings to improve the system
☐ Having external quality audits by an accredited certification body to improve the system
☐ Having a 'post approval' discussion with the sponsor to provide feedback on the quality of the dossier and obtain the company's comments

Management responsibility for quality

4.2.3 Does the agency have a dedicated department for assessing and/or ensuring quality in the assessment and registration process?

☐ YES ☐ NO

4.2.4. ***If YES****, how many staff are involved?*

Click or tap here to enter text.

4.2.5 How often do you assess and/or ensure quality in the assessment and registration process?

☐ Annually
☐ Semi-annually
☐ Ad hoc
☐ Other, please specify: Click or tap here to enter text.

4.2.6 To whom does this section report (e.g., the Chief Executive Officer of the agency)?

Click or tap here to enter text.

4.2.7 ***If NO*** *to 4.2.3, is the agency thinking of setting up such a department?*

☐ YES ☐ NO

4.3 Quality in the Review and Assessment Process

Improving the quality of applications

4.3.1 Does the agency have official guidelines to assist industry in the registration of medicinal products?
☐ YES ☐ NO

4.3.2 ***If YES,*** *how are these guidelines made available? (Please indicate all that apply)*

☐ Through the agency's website
☐ Through official publications
☐ On request
☐ Through Industry associations
☐ Other, please specify: Click or tap here to enter text.

4.3.3 What language/s are the guidelines available in?

☐ Local language only
☐ English
☐ Other, please specify: Click or tap here to enter text.

Improving quality through interactions with applicants

4.3.4 Does the agency provide pre-submission scientific advice to applicants?

☐ YES ☐ NO

4.3.5 ***If YES,*** *how is the quality of that advice monitored?*

Click or tap here to enter text.

4.3.6 Is the applicant given details of technical staff that can be contacted to discuss an application during review?

☐ YES ☐ NO

4.3.4 Please indicate which of the following best describes the level of contact that companies have with agency staff or outside experts during development and during the agency's assessment:

	Development	**Assessment**
• Extensive formal contact (including scheduled meetings)	☐	☐
• Extensive informal contact (frequent telephone or email contact)	☐	☐
• Some formal contact (possibility of meetings)	☐	☐
• Some informal contact (possibility of telephone or email contact)	☐	☐
• None, or minimal formal contact (rare occurrences of contact, via letter or fax)	☐	☐
• None, or minimal informal contact (rare telephone or email contact)	☐	☐

4.3.5 Please comment on general policy for contact with applicants:

Click or tap here to enter text.

Scientific Committee Procedures

If your review procedure includes obtaining the advice of a scientific committee of internal and/or external experts (as in Section Review by Scientific Committee) please complete the following:

4.3.6 Name of the Committee :

Click or tap here to enter text.

4.3.7 Number of Committee members :

Click or tap here to enter text.

4.3.8 How frequently does the Committee meet?

☐ Once a week
☐ Once a month
☐ Other, please specify: Click or tap here to enter text.

4.3.9 For NAS applications and major line extensions does the Committee review:

☐ All applications
☐ Selected dossiers, please specify: Click or tap here to enter text.

4.3.10 Does the Committee review:

☐ The complete dossier
☐ Assessment reports from the reviewers

Shared and Joint reviews with other Regulatory Agencies outside of your country

A ***shared review*** is "*one where each participating agency takes responsibility for reviewing a separate part of the dossier*". A ***joint review*** is "*one where the whole dossier is reviewed by each agency and the outcome is discussed before a decision is taken*" (see Glossary).

4.3.11 Is your agency part of any regional alignment initiatives?

☐ YES ☐ NO

*4.3.12 **If YES**, please specify and complete Appendix II:*

Click or tap here to enter text.

4.3.13 Are bilateral/multilateral information sharing agreements in place with other jurisdictions?

☐ YES ☐ NO

*4.3.14 **If YES**, what is the general nature of those agreements?*

Click or tap here to enter text.

4.3.14 Does your agency conduct shared or joint reviews with other regulatory authorities?

☐ YES, regularly. Please state which authorities: Click or tap here to enter text.

☐ YES, occasionally. Please state which authorities: Click or tap here to enter text.
☐ NO, this has never been undertaken

4.3.15 If YES, do you have formal measures in place to ensure consistent quality during the review?

☐ YES ☐ NO

*4.3.16 If **YES**, please specify:*

Click or tap here to enter text.

*4.3.17 If **NO**, do you anticipate undertaking such reviews within the next two years?*

☐ YES ☐ NO

4.3.18 Have these joint reviews influenced the way in which your agency conducts reviews in general?

☐ YES, please specify: Click or tap here to enter text.
☐ NO

4.4 Training and continuing education as an element of quality

The following questions relate to training and continuing education of assessors working within the agency, including those employed on a full-time basis and those contracted for specific assessments were necessary.

4.4.1 Do you have a formal training programme for assessors?

☐ YES ☐ NO

4.4.2 Which of the following methods are used for training assessors?

☐ Induction training
☐ On job training
☐ External courses
☐ Post-graduate degrees
☐ Placements and secondments in other regulatory authorities
☐ External speakers invited to the agency
☐ Participation in international workshops/ conferences
☐ In-house courses
☐ Other, please specify: Click or tap here to enter text.

4.4.3 Do you have a formal training programme for assessors?

☐ YES ☐ NO

Collaboration with other agencies

4.4.4 Does your agency seek direct assistance of more experienced agencies for development of SOPs and Guidelines?

☐ YES ☐ NO

*4.4.5 If **YES,** please give details:*

Click or tap here to enter text.

4.4.6 Does your agency mainly develop SOP, Guidelines etc., based on information published by more experienced agencies:

☐ YES ☐ NO

4.4.7 Does your agency collaborate with other agencies in the training of assessors?

☐ YES, please specify: Click or tap here to enter text.
☐ NO

Completion of training

4.4.8 Is training tested in examination situations once completed?

☐ YES
☐ NO
☐ Partly

4.4.9 Is completion of training courses required for professional advancement?

☐ YES
☐ NO
☐ Partly

4.5 Transparency of the review process

This section examines 'transparency' in terms of the ability and willingness of the agency to assign time and resources to providing information on its activities to both the informed public (which includes health professionals) and industry.

4.5.1 What priority does your agency assign to being open and transparent in relationships with the public, professions and industry?

☐ High priority
☐ Medium priority
☐ Low priority

Please comment: Click or tap here to enter text.

4.5.2 What are the main drivers for establishing transparency? Please indicate the top three incentives for assigning resources to activities that enhance the openness of the regulatory system:

☐ Political will
☐ Public pressure
☐ Press and media attention
☐ Need to increase confidence in the system
☐ Need to provide assurances on safety safeguards
☐ Better staff morale and performance
☐ Other, please specify: Click or tap here to enter text.

Transparency to the public

The following questions explore the availability of information to the general public on the performance of regulatory authorities.

4.5.3 Please indicate which of the following information items about the assessment and registration of marketing applications is available to the public:

☐ Approval of products
☐ Approval times
☐ Summary of the grounds on which the approval was granted
☐ Advisory Committee meeting dates
☐ Other, please specify: Click or tap here to enter text.

4.5.4 How is this information made available?

☐ Official journal/periodical publication
☐ From an official Internet website
☐ On request
☐ Other, please specify: Click or tap here to enter text.

Transparency to companies on the application progress

4.5.5 Are companies able to follow the progress of their own applications?

☐ YES ☐ NO

4.5.6 If YES, please indicate the mechanisms available to industry:

☐ Telephone contact
☐ Electronic access to the status of applications
☐ E-mail contact
☐ Other, please specify Click or tap here to enter text.

4.5.7 Are companies given detailed reasons for rejection of an application for registration?

☐ YES ☐ NO

Facilities for providing information

4.5.8 Is there an electronic system for registering and tracking applications?

☐ YES ☐ NO

4.5.9 ***If YES****, please indicate whether it has the following capabilities:*

☐ Tracking applications that are under review and identifying the stage in the process
☐ Signalling that target review dates have been exceeded
☐ Recording the terms of the authorisation once granted
☐ Archiving information on applications in a way that can be searched

4.5.10 ***If NO,*** *are there plans to introduce such a system?*

☐ YES ☐ NO

4.5.11 ***If so****, please give target date for implementation:*

Click or tap here to enter text.

PART 5. QUALITY DECISION-MAKING PROCESSES

Regulatory agencies consider various types of information needed to carry out their assessment of new medicines, but it is not always clear how the decisions, which require human judgment and interpretation, are made around the data. According to the well-established principles of the science of decision making, any organisation that seeks to improve its productivity and consistency should also routinely measure the quality of its decision-making process. These questions aim to uncover the decision-making practices of your agency, focusing on the process to approve or reject a New Drug Application.

5.1 Decision-making frameworks

A Framework is "*a set of principles, guidelines and tools which provide a structured systematic approach to guide decision-makers in selecting, organising, understanding and summarising subjective values and judgments that form the basis of a decision, as well as communicating the evidence relevant to the decision*" (see Glossary).

5.1.1 Does your agency have a framework in place that forms the basis of the decision to approve or reject a New Drug Application (NDA)?

☐ YES ☐ NO

If "No", please answer 5.1.2-5.1.3, and then go to 5.2, if "Yes", please go to section 5.1.4 and continue

5.1.2 Why a framework is not used? (mark all that apply)

☐ Lack of a validated framework
☐ Lack of knowledge/training on decision making in general
☐ Benefits of a framework not apparent
☐ Resource/administrative limitation
☐ Others, please specify: Click or tap here to enter text.

5.1.3 Are there plans to adopt a framework in the next two years?

☐ YES
☐ NO
☐ Not sure

5.1.4 Which statement best describes the nature of your framework?

☐ The framework has been formally defined and codified
☐ The framework is informal, by custom and practice (i.e. it has never been clearly agreed but over time has become the process)

5.1.5 In your view, which Quality Decision-Making Practices have been implemented into your agency's framework (to approve/reject an NDA) and are they adhered to in practice?

See the Appendix I for explanation on the Practices.

Practice	Implemented into framework (select one)			Adhered to in practice (select one)		
	Fully	Partially	Not	Fully	Partially	Not
1. Have a systematic, structured approach (consistent predictable and timely)	☐	☐	☐	☐	☐	☐
2. Assign clear roles and responsibilities (decision makers, advisors, information providers)	☐	☐	☐	☐	☐	☐
3. Assign values and relative importance to decision criteria	☐	☐	☐	☐	☐	☐
4. Evaluate both internal and external influences/biases	☐	☐	☐	☐	☐	☐
5. Examine alternative solutions	☐	☐	☐	☐	☐	☐
6. Consider uncertainty	☐	☐	☐	☐	☐	☐
7. Re-evaluate as new information becomes available	☐	☐	☐	☐	☐	☐
8. Perform impact analysis of the decision	☐	☐	☐	☐	☐	☐
9. Ensure transparency and provide a record trail	☐	☐	☐	☐	☐	☐
10. Effectively communicate the basis of the decision	☐	☐	☐	☐	☐	☐

5.1.6. Please comment and provide examples

Click or tap here to enter text.

5.2 Decision-making challenges

5.2.1 In your opinion, does your agency have measures in place to minimise impact of subjective influences / biases on your agency's decision making for the process to approve/reject an NDA.

Please see the Glossary for more explanation on biases.

☐ YES ☐ NO

Comment: Click or tap here to enter text.

5.2.2 Are there formal assessments in place to periodically measure the quality of decision-making within your agency for the process to approve/reject an NDA?

☐ Yes, and this is to measure the quality of the process of decision making
☐ Yes, and this is to measure the quality of the outcome
☐ No

Comment: Click or tap here to enter text.

5.2.3 Does your agency provide training in the area of quality decision making?

☐ YES ☐ NO

Comment: Click or tap here to enter text.

5.2.4 Do you think that your agency's decision-making process for approving/rejecting an NDA could be improved?

☐ YES ☐ NO

Comment: Click or tap here to enter text.

PART 6. CONCLUDING OBSERVATIONS

The purpose of the following two questions is to try to identify the Agency's own perception of its unique positive qualities and the major impediments it faces in carrying out the review of new medicines and making them available to meet patients' needs.

6.1 List three factors that make a major contribution to the effectiveness and efficiency of your agency's review procedures and decision-making processes for NAS applications:

1. Click or tap here to enter text.
2. Click or tap here to enter text.
3. Click or tap here to enter text.

6.2 List three factors that act as barriers to making new medicines available in a timely manner through the regulatory process:

1. Click or tap here to enter text.
2. Click or tap here to enter text.
3. Click or tap here to enter text.

6.3 Are there any important documents related to GRevP that you would like to share with CIRS?

☐ YES ☐ NO

6.4 If yes please list and provide directly to CIRS:

Click or tap here to enter text.

ACKNOWLEDGEMENT

This questionnaire has been completed by: Name…….

Postion…….. Agency……

Date……..

Thank you for completing this questionnaire

GLOSSARY AND ABBREVIATIONS

Additional information	Additional data or additional analyses of existing data requested from the sponsor by the regulatory agency during the review process.
Advisory Committee	An expert committee that advises the regulatory agency of the safety, quality and efficacy of new medicines for human use.
Approval	The approval of a drug product by a regulatory agency, signified by the granting of a marketing authorisation, or the issue of a technical approval letter. However, the product may still not be marketable until negotiations for pricing and reimbursement are concluded.
Assessment template	Set out the content and format of written reports on scientific reviews
Bias	A subjective influence. Different types have been identified for example: · Action-oriented influences drive us to take action less thoughtfully than we should e.g. Excessive optimism, overconfidence, gut-feeling · Interest influences arise in the presence of conflicting incentives and even purely emotional ones. E.g. misaligned individual incentives and attachments · Pattern-recognition influences lead us to recognize patterns even where there are none e.g. confirmation bias to seek out information that supports a favoured decision · Stability influences create a tendency toward inertia in the presence of uncertainty e.g. preference for the status quo in the absence of pressure to change it *Source: Lovallo and Sibony*
Certificate of Pharmaceutical Product (CPP)	Certificate issued in the format recommended by the World Health Organization (WHO), which establishes the status of the pharmaceutical product and of the applicant for this certificate in the exporting country.
Chemistry, manufacturing and controls (CMC)	All activities conducted to optimize, scale-up and validate the processes and technologies for transfer to manufacture and all Quality Assurance (QA), Quality Control (QC) and Chemistry, manufacturing and controls support activities (e.g. CMC project management including CMC contribution to project teams). This includes all drug substance R&D i.e. process research and process development, all drug product R&D i.e. formulation development and process development, all analytical work for drug substance R&D and drug product R&D, clinical supplies and CMC's involvement in the compilation of regulatory documentation.

Clinical summary	Summary of clinical study data that typically includes biopharmaceutic studies and associated analytical methods, clinical pharmacology studies, clinical efficacy, clinical safety, literature references, and synopses of individual studies. Refers to Module 2.7 in CTD format.
Common Technical Document (CTD) format	Common technical document (CTD) as outlined in the ICH guideline M4 (Organisation of the common technical document for the registration of pharmaceuticals for human use; M4).
Framework	A set of principles, guidelines and tools which provide a structured systematic approach to guide decision-makers in selecting, organising, understanding and summarising subjective values and judgments that form the basis of a decision, as well as communicating the evidence relevant to the decision
Good Clinical Practice (GCP)	An international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. It aims to provide a unified standard for the ICH regions to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.
Good Review Practices (GRevP)	A code about the process and the documentation of review procedures that aims to standardise and improve the overall documentation and ensure timeliness, predictability, consistency and high quality of reviews and review reports.
Internal reviewers	Internal reviewers are employees of the agency
International Conference on Harmonisation (ICH)	Brings together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration.
Joint review	The whole dossier is reviewed by each agency and the outcome is discussed before a decision is taken.
Major Line Extension (MLE)	A major line extension is a modification to an authorised Medicinal Product that is sufficiently great that it cannot be considered to be a simple variation to the original product, but requires a new product authorisation. Such modifications include major new therapeutic indications or new disease states, extension to new patient populations (e.g., paediatrics), a new route of administration or a novel drug delivery system.
Marketing Authorisation	Authorisation issued by a regulatory to launch a drug product on the market.
Marketing Authorisation Application (MAA)	Authorisation application submitted to a regulatory agency to launch a drug product on the market to which the application has been submitted

Milestone	A milestone must involve some form of dated written document to which the regulatory agency can refer. In addition, a milestone must be considered by the regulatory agency to be the point at which one event stops and the next one begins so that the times for events are interdependent.
New Active Substance (NAS)	A new chemical, biological or pharmaceutical active substance includes: · a chemical, biological or radiopharmaceutical substance not previously authorised as a medicinal product; · an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance not previously authorised as a medicinal product but differing in properties with regard to safety and efficacy from that chemical substance previously authorised; · a biological substance previously authorised as a medicinal product, but differing in molecular structure, nature of the source material or manufacturing process; a radiopharmaceutical substance which is radionucleotide, or a ligand not previously authorised as a medicinal product, or the coupling mechanism to link the molecule and the radionucleotide has not been previously authorized.
Non-clinical summary	Summary of non-clinical data including: pharmacology, pharmacokinetics and toxicology. Refers to Module 2.6 in CTD format.
Peer review	Peer review means an additional evaluation of an original assessment carried out by an independent person or committee. Peer review can occur either during assessment of a dossier, or at sign-off.
Quality control (QC)	Quality control is operational techniques and activities that are used to fulfil requirements for quality. It involves techniques that monitor a process and eliminate causes of unsatisfactory performance at all stages of the quality cycle.
Quality policy	Overall intentions and direction of an organisation related to quality as formally expressed by top management.
Questions to sponsor	The process of asking the sponsor for additional data or additional analyses of existing data. The requests are made by the regulatory agency during the review process.
Scientific assessment	Review of the dossier in terms of safety, quality and efficacy of data submitted.

Shared review	Each agency takes responsibility for assessing a separate part of a dossier.
Sponsor	A company, person, organisation or institution that takes responsibility for initiating, managing or financing a clinical study.
Standard Operating Procedures (SOPs)	Detailed, written instructions to achieve uniformity of the performance of a specific function
Validation of a dossier	The process whereby the agency verifies that all parts of the submitted dossier are present and complete and suitable to be assessed as part of the assessment and registration process.

APPENDIX I – QUALITY DECISION-MAKING PRACTICES

Transparency • Predictability • Consistency

Development of the 10 Quality Decision-Making Practices

As a result of the discussion from CIRS Workshops in June 2015 and February 2016[3], the following Guidance Notes were produced to describe the 10 QDMPs in more detail.

QDMP 1. Have a systematic, structured approach to aid decision making (consistent, predictable and timely)

- *Establish the decision context, objectives and assumptions made.*
- *Employ frameworks, guidelines and tools for structuring the decision-making process.*
- *Such an approach should ensure that the process is systematic, which in turn would enable better consistency compared with similar past decisions, as well as predictability and timeliness.*

QDMP 2. Assign clear roles and responsibilities (decision makers, advisors, information providers)

- *The roles and responsibilities should be clearly defined in terms of individuals who provide information (including external input), compared with those who advise on the decision or make the final decision.*
- *The roles and responsibilities of each stakeholder (regulatory authorities, HTA agencies and companies) should be transparent and well communicated, which should help manage expectations.*

QDMP 3. Assign values and relative importance to decision criteria

- *The relevant criteria for the decision must be determined to ensure that these are in line with the decision context and overall objective. The criteria should be weighted, for example, by ranking or rating their relative importance.*

QDMP 4. Evaluate both internal and external influences/biases

- *Stakeholders need to be aware of personal considerations, subjective influences and biases, acknowledge them and minimise where possible. Potential biases that need to be considered[4]:*
  - *Action-oriented bias: excessive optimism, overconfidence in own judgement and gut-feeling*
  - *Interest-oriented bias: inappropriate attachments and misaligned incentives*
  - *Pattern recognition: generalising based on recent events and seeking out information that supports a favoured decision, which could lead to perpetuating previous mistakes*
  - *Stability bias: preference for status quo and tendency for inertia in the presence of uncertainty*

QDMP 5. Examine alternative solutions

- *Decision makers should actively explore possible options during the decision-making process.*
- *The alternatives need to be assessed, for example using a SWOT analysis, against the relevant decision criteria in order to determine the best outcome.*

QDMP 6. Consider uncertainty

- *The extent and limitations of available information need to be judged for each decision criterion in relation to the alternative options.*
- *Stakeholders must be explicit regarding acceptability of benefits and harms and how this affects their approach.*

QDMP 7. Re-evaluate as new information becomes available

- *This should be actively carried out at all stages during the lifecycle of medicines' development.*
- *This may be a safeguard against plunging in or procrastination and/or perpetuating previous mistakes as well as identifying cultural/organisational/hierarchical influences (e.g. individual vs. organisational, group successes and group failures).*

QDMP 8. Perform impact analysis of the decision

- *The impact of the decision needs to be considered on both internal and external stakeholders.*
- *The analysis must relate to present situation, but also to the future and should take into account elements of quality/validity of data, political/financial/competitor influences and procedures for similar decisions.*

QDMP 9. Ensure transparency and provide a record trail

- *It must be clear how the decision was made and details must be consistently documented in a manner that can be easily followed or audited by appropriate stakeholders.*

QDMP 10. Effectively communicate the basis of the decision

- *The basis of the decision needs to be appropriately communicated to the relevant stakeholders, both internally and externally.*

[3] The Centre for Innovation in Regulatory Science. *Publications*. Available at: http://www.cirsci.org/past-workshops-and-publications/

[4] Lovallo D, Sibony O. *The case of behavioral strategy*. McKinsey Quarterly. Available at: http://www.mckinsey.com/insights/ strategy/ the_case_for_behavioral_strategy.