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

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Abstract

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

Methods: An exploratory mixed-method design using both qualitative and quantitative data, was employed. Data was collected from six national medicines regulatory authorities (NMRAs) and the EAC Secretariat through a combination of semi-structured interviews, questionnaires, and checklists for the period 2011/12-2014/15 while 2010/11 data served as baseline. Interviews were conducted with heads of NMRAs; regulatory and monitoring and evaluation experts; and the EAC Secretariat Project Officer. A set of 29 indicators grouped into 9 categories were used to measure NMRAs performance.

Results: policy and legal frameworks provide a foundation for effective regulation. Collaboration, harmonization, joint dossier reviews and inspections of manufacturing sites; reliance and cooperation are key factors for building trust and capacity among NMRAs. 83.3% of the EAC Partner States have comprehensive medicines laws with autonomous NMRAs. All the NMRAs have functional registration and good manufacturing practice inspection systems supported by regional harmonised guidelines for registration, inspection, quality management and information management systems with 80% attaining ISO 9001:2015 certification. Efficiency of registration processes improved by 66.6%.

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

Background

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

The advent of African Continental Free Trade Area (AfCFTA) marks a momentous milestone for economic integration in Africa aiming to boost intra-African trade by making Africa a single market of 1.2 billion people and a cumulative gross domestic product (GDP) of over $3.4 trillion across the 55 member states of the African Union (AU) [5][6]. The health care and wellness sector is estimated at $259 billion by 2030, the $45 billion projection of the African pharmaceutical market by 2020, attributed to the changing economic profiles, rapid urbanization,

increased healthcare spending and investment, and increasing incidence of chronic lifestyle diseases [7,8]. The increasing demand of medicines in Africa due to population and economic growth as well as raising consumer awareness warrants governments' investment in local production and regulation of medical products [6,9].

For many years the capacity to regulate medicine in Sub-Saharan African countries has been confronted with fragmented legal frameworks, weak management structures and processes, and a severe lack of staff and resources which affect countries' with subsequent proliferation of substandard and falsified medicines in various markets [10-11]. Reports have revealed that 7% of the 46 sub-Saharan African countries have moderately developed medicine regulatory capacity, about 63% have minimal capacities and the remaining 30% do have an NMRA in place [12]. In addition; poor inspection practices; ineffective licensing and product registration systems; inadequate access to quality control laboratories; non-existent pharmacovigilance, clinical trials oversight and drug promotion control systems; with subsequent 30% product quality failure rates; are characteristic of regulatory systems in Africa [13]. This is coupled with inadequate communication and information exchange systems, a lack of transparency and accountability and conflict of interest [13]. A study conducted in the 54 African Union (AU) Member States revealed that except for Sahrawi Republic, all the remaining 53 countries have NMRAs with varying organizational setup and level of functionality [14]. While some operate as units or departments within Ministries of Health, others are semi- or fully autonomous agencies [14].

There is need for governments and partners to build and strengthen medicines regulatory systems across the African continent to ensure that countries have appropriate institutions with legal mandate, quality management systems, human and financial resources, the needed infrastructure and enforcement systems to carry out regulatory functions [13]. It is also important for NMRAs to collaborate with other agencies and participate in regional medicines regulatory harmonization initiatives as a way of building their capacity [13]. Effective and efficient regulation of medical products provides an opportunity for investment in manufacturing, trade and sale of pharmaceutical products; and increased research and development of new medical products and technologies; with consequent social and economic benefits to the patients [15–17]. Building medical products regulatory capacity is also crucial for achieving Universal Health Coverage (UHC) goals; the African Union (AU) Agenda 2063 aspirations and goals 1 and 3; as well as Sustainable Development Goals (SDGs) on access to quality, safe and efficacious health products to the people [17].

In recognition of regulatory capacity limitations in Africa, various initiatives are being undertaken to address this problem with positive results being recorded in the area of product registration, good manufacturing practice (GMP) inspections, quality control, post-marketing surveillance, pharmacovigilance and clinical trials oversight [15,16]. The African Medicines Regulatory Harmonization (AMRH) Initiative, the African Vaccines Regulatory Forum (AVAREF), the Network of Official Medicines Control Laboratories in Sub Saharan Africa (NOMCOL-SSA) and the World Health Organization Prequalification of Medicines (WHO-PQ) Programme have invested in building regulatory capacity in Africa [15,17][22-26]. Over the years, the WHO-PQ has provided hands-on training for assessors and inspectors of low- or middle-income countries to build their capacity [17]. This is done through participation in assessment of finished pharmaceutical products (FPPs) and active pharmaceutical ingredients (APIs) and collaborative procedure for accelerated registration of medical products [17]. The AMRH Initiative on the other hand is an attempt by the AU to strengthen regulatory capacity, encourage harmonization of regulatory requirements and expediting access to quality, safe, and effective medicines for patients in need in Africa [18]. The Initiative is implemented as part of the AU PMPA policy framework to provide an enabling regulatory environment for local production and contribute to UHC, AU Agenda 2063 and SDGs goals [15-16].

Through the AMRH Initiative, countries in the East African Community (EAC) and the Southern African Development Community (SADC) using the Zazibona collaborative procedure, have recorded significant improvements in registration timelines from the average 2-7 years to a median of 7 months [20-21]. The initiative is also implemented in the Economic Community of West African States (ECOWAS), Intergovernmental Authority on Development (IGAD) and Economic Community of Central African States (ECCAS). With more than 85% of countries in Sub-Saharan Africa at different levels of implementation of medicines regulatory harmonization Programmes. In order to address the problem of non-coherent medicines laws in African countries, the AMRH Initiative developed a Model Law on Medical Products Regulation to ensure effective regulation and promote harmonization [21,27]. The Model Law which promotes the establishment of autonomous agencies with powers to make independent regulatory decisions and to collect and utilize fees for regulatory services was adopted by the AU Assembly in January 2016 and has been domesticated by more than 12 AU Member States [21]. Eleven (11) regional centres of regulatory excellence have been designated since 2014 to provide coordinated and structured regulatory science training programme using existing academic institutions in partnership with regulatory agencies to ensure sustainable production of the regulatory workforce in Africa [21].

Harmonizing regulatory standards across countries; work and cost-sharing arrangements and collaboration between NMRAs; coupled with advocacy and information campaigns are key for addressing the existing limitations, increasing visibility on the importance of effective regulation of medical products and its contribution to public health and economic development [21]. The AMRH provides a platform to support regional economic communities (RECs), regional health organizations (RHOs) and Member States in harmonizing medicines regulation and regulatory capacity strengthening by mobilizing interested governments, donors and other stakeholders to invest in medicines regulation [19][21]. the AMRH Initiative serves as a foundation for the establishment of the African Medicines Agency (AMA) as enshrined in the AU Executive Council Decision EX.CL/872(XXVI) of January 2015 [21][32]. It is expected that these initiatives will accelerate the development of new or improved medical interventions for poverty-related neglected diseases (PRNDs); provide an enabling environment for manufacturing; and contribute towards the African Union Agenda 2063 and the global 2030 sustainable development goals [16][21].

Understanding the relevance of various regulatory interventions undertaken at country, regional and continental levels is important for informing regulatory policy reforms undertaken by the AU, governments, and partners [28]. It is for this reason that a study to evaluate the effect of medicines regulatory harmonization initiative in the East African Community region was undertaken to provide insights on whether it is making an impact on national regulatory capacity. The study aimed to determine factors which have attributed in improving regulatory capacity in the EAC NMRAs. Specifically; the study focused on the level at which countries have; i) implemented agreed common technical document (CTD) for registration of medicines in the EAC Partner States; ii) implemented common information management systems for medicines registration in each of the EAC Partner States' NMRAs, and whether or not the country information management system (IMS) is linked in all Partner States and EAC Secretariat; iii) implemented quality management systems (QMS) in each of the EAC Partner States' NMRAs; iv) the level of capacity attained at regional and national levels to implement medicines registration harmonization in the EAC region; v) whether or not a framework for mutual recognition procedure has been developed and implemented in the East African Community Partner States; and lastly vi) whether or not a platform for information sharing with key stakeholders at national and regional level has been established. The research hypothesis is that the EAC MRH Project implemented under the AMRH Initiative has increased regulatory capacity in the EAC Partner States.

Methods

Study design: An exploratory, mixed method design using both qualitative and quantitative data, was employed in this study. Data was collected from all the six NMRAs in the EAC partner States namely, the Republic of Burundi, Republic of Kenya, Republic of Rwanda, the United Republic of Tanzania (with two NMRAs), and the Republic of Uganda. Data from six NMRAs was collected through a combination of semi-structured interviews, questionnaires and checklists **(as indicated in S1 Table),** for the period 2011/12-2014/15 while 2010/11 data served as baseline. Questionnaire and checklist were developed based on the information obtained from the preliminary situational analysis study [29,30]. Moreover, additional questions were adopted from the WHO Global benchmarking tool for evaluation of national regulatory systems [31]. Validation of the questionnaire and checklists was done using a pilot study.

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

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

Data analysis: Arithmetic means and standard deviations were determined for all numerical data across all years for each individual respondent NMRA. Observations were also made on the presence of any trend in the course of time from the baseline to the end of the study duration. Where only a single point data was provided by the respondents, it was reported as such. Due to lack of data from some agencies, only the available data set was used in statistical analysis and interpretation. Categorical (Non-numerical) data were reported and analysed as Yes or No, with the specific year of their first appearance being noted and indicated in the parenthesis in the tables of results. All data were finally summarized using tabulation of the identified indicators against each of the NMRAs, arranged in a side by side order for easy comparison and comprehension. Evaluations were made on the consistency and trends of each indicator across the NMRAs and years under study.

To measure the performance of regional medicines regulatory harmonization initiatives and to ensure objective assessment of the EAC MRH initiative, 29 indicators were developed and grouped into 9 main categories as indicated in indicators matrix **Table 2.1**. Each indicator was further refined and validated to facilitate users' understanding, to ensure accuracy of data collected and objective analysys. This was done through validation workshops with monitoring and evaluation focal points from the EAC NMRAs, RECs and WHO.

Results

For the purpose of this paper, findings are categorised into five (5) main catogories namely policy and legal framework; NMRA governance; medicines registration and good manufacturing practice (GMP) systems; quality management systemss and information management systems.

Figure 3. 1: The Status of National Medicines Policies and Medicines Laws in the EAC region; 2010/11 – 2015/2016

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

Governance: A baseline study revealed that, TMDA, ZFDB and Kenya Pharmacy and Poisons Board (PPB) were semi-autonomous entities and that the head of PPB also served as a Chief Pharmacist combining both regulatory and policy roles as the technical arm of the Ministry of Health [29,30]. For Rwanda and Burundi, regulatory functions were administered by the respective Ministries of Health Departments. For TMDA (Tanzania), KPPB (Kenya) and the NDA (Uganda), the agencies had powers to charge fees for regulatory services and received very little or no government subvention [29,30].

This study has shown a significant improvement in the level of autonomy of NMRAs. Currently; four (4) NMRAs are operating as semi-autonomous agencies namely; the Rwanda Food and Drugs Authority (RFDA), TMDA (for Tanzania mainland), Zanzibar Food and Drug Agency (ZFDA), Kenya Pharmacy and Poisons Board; while Uganda National Drugs Authority (NDA), is fully autonomous. Furthermore, the National Pharmaceuticals Regulation Law of Burundi which was under consideration by the national Parliament provides for the establishment of a semi-autonomous NMRA to be called Drug and Food Regulatory Authority of Burundi (ABREMA) [44]. **Table 3.2** provides analysis of the NMRAs governance framework including the level of autonomy.

There is a progressive trend in the development of regulations and guidelines in the EAC Partner States **(Table 3.3 and Figure 3.2).** While baseline data showed three out of the six (50%) NMRAs had regulations and guidelines, in end-line data, 5 of 6 NMRAs (83%) reported having regulations and guidelines in place.

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

Figure 3. 2 Trends in developing regulations and guidelines in the EAC Partner States (excluding Burundi); 2011/12 – 2014/15

Medicines registration system: Comparison of baseline data show improvement in registration system in Rwanda and Burundi. All the six (6) NMRAs now have a legal mandate to register medicines and have a system to manage applications from receipt of dossier to the issuance of marketing authorization. In addition, all the NMRAs use the EAC harmonized guidelines for registration and standard operating procedures (SoPs) for joint review of dossiers. All NMRA participate in the EAC joint review of dossiers. However, the time taken to register a product based on the outcome of the joint review process varies from country to country. For instance, out of fifteen (15) applications which were received through the regional procedure, TMDA registered all the products; KPPB 13/15; Burundi 1/15; Rwanda 9/15; Zanzibar 1/15, and Uganda 7/15. There is need to study factors hampering national uptake of joint review process as it has an impact on marketing authorization timelines. Reliance mechanisms exist in Kenya, Tanzania-Mainland, Tanzania-Zanzibar and Uganda while it was not the case for Burundi and Rwanda.

GMP Inspection System: All six (6) NMRAs have a legal mandate to conduct GMP inspection. Except for Burundi NMRA, all the remaining NMRAs reported conducting inspections of manufacturing sites. While Kenya, Tanzania and Uganda NMRAs have conducted inspections since baseline study, Rwanda and Zanzibar NMRAs only started

in 2015. With exception of Burundi, all the NMRAs indicated using EAC Harmonized guidelines for GMP inspection from 2015 when they came into force. Each NMRA reported having participated at least once in the EAC joint inspections. Rwanda, Uganda and Zanzibar employ a reliance models by using GMP inspection reports from other ag such as EAC, SRAs, PICs, US-FDA, and/or WHO-PQ Programme. **Table 3.4** is a detailed analysis of the status of registration and GMP inspection system in the 6 NMRAs in the EAC region.

Table 3. 4 Medicines Registration and GMP Inspection Systems in the EAC Partner States NMRAs; 2011/12 – 2015/16

Table 3.5 provides detailed results on the status of each of the EAC NMRAs system for registration of medicines. The highest five years average of 800 new applications were received by the Tanzania-Mainland NMRA, followed by Uganda (458), Burundi (70) and Zanzibar (16). There was no data for Kenya and Rwanda for the reported period.

Table 3. 5 Medicines Registration System in the EAC Partner States NMRAs; 2011/12 – 2015/16

Secondary data shows that with the initial target to have 75 medicines registered by TFDA, NDA & PPB by end of yr 5, the 3 NMRAs have exceeded the target with their respective numbers indicated in brackets, TMDA (237), Kenya PPB (1676) and Uganda NDA (612) [45]. With a target of 100 applications to be submitted to NMRAs using EAC CTD by end of yr 5; TMDA had received 1266 applications, Uganda NDA-2147; Kenya PPB-2475; ZFDA-76; PTF-792; and DPML -447. For EAC NRAs with limited capacity, the target was to register 50 products and the outcome is as follows; ZFDA (42), which is 85 % of the target, PTF registered 297 i.e. over 100% of target while DPML registered 10 products (20% of the target).

Report of the joint review process shows that out of the forty-nine (49) applications received, 38 applications were jointly evaluated including eight (8) Anti-Cancer, Anti-TB and Anti-Biotics. The products include Avastin Inj (100/4ml,400/16ml); Herceptin injection (150mg & 440mg); Nexavar Tabs 200mg; Sirturo Tabs 100mg; Cetuximab 5mg/ml (Soln for Infusion); and Kemoxyl DT 250 Disp Tabs and they granted marketing authorization withing 5-7 months following receipt of the application [66]. In addition, all the EAC Partner States NMRAs domesticated the EAC GMP Guideline and conducted fourteen (14) Joint GMP Inspections in various countries including Egypt, Kenya, India, Uganda, Tanzania, and Morocco with ten (10) facilities meeting GMP Standards and issued with Certificate of Compliance [45]. The median timeline from dossier submissions to national marketing authorization in the EAC region was reduced to seven (7) months since implementation of joint dossier assessments compared to the previous 1 – 2 years [19].

Functional information management systems: One of the EAC MRH Objectives is to have all the Partner States' NMRAs implementing common information management system (IMS) for medicines registration in each of the EAC Partner States' NMRAs which is linked in all Partner States and the EAC Secretariat. A robust IMS is key for supporting the technical aspects of medicines regulation to facilitate efficiency and effectiveness of business processes, improve transparency; facilitate decision-making process, sharing and exchange of information among NMRAs and stakeholders; and timeliness of approval of registration decisions. During the baseline survey in 2010/11, Tanzania-Mainland had an integrated system which was locally developed, and Kenya used SIAMED®. Uganda, on the other hand, used a combination of SIAMED®, ACCESS® and a locally developed software. Burundi had a manual IMS which was not functioning, Zanzibar had a functional manual registry and Rwanda had both a manual and electronic system. The method of capturing information in NMRA's in the EAC Partner States was variable and unreliable, the electronic systems were not user friendly, they were difficult to integrate with other IMS

platforms and could not automatically generate/print certificates or be linked to websites, and the manual systems were labour intensive.

A comparison of IMS implementation status with baseline data shows a significant improvement in all the countries with Burundi and Zanzibar moving from manual to electronic systems. All the EAC NMRAs are now using a harmonized IMS with 5 out of 6 NMRAs sharing regulatory information amongst each other as indicated in **Table 3.6 and Figure 3.3.**

Table 3. 6 Different Levels of IMS Implementation by the EAC Partner Sates NMRAs; 2011/12 – 2015/16

Figure 3. 3 The Status of Implementation of Information Management Systems in the EAC Partner States NMRAs (2016)

Table 3. 7 Information Management System in the East African Community Partner States National Medicines Regulatory Authorities (2016)

Functional quality management system: ISO certification is a globally recognized accreditation of the maturity and functionality of the quality management system (QMS) of an organization, including medical products regulatory agencies. EAC MRH Projects advocates for implementation of QMS to facilitate delivery of quality and consistent services to customers. Zanzibar, Burundi, Rwanda and Kenya had no QMS during baseline survey, TMDA was ISO 9001:2008 certified and Uganda had initiated the ISO certification process. Evaluation of QMS implementation data from the EAC Partner States NMRAs indicated different levels of implementation as indicated in **Table 3.7.**

Table 3.7 Functional Quality Management System in the EAC Partner States NMRAs; 2011/12 – 2014/15

To date, Kenya, Tanzania, Zanzibar and Uganda's NMRAs are 9001:2015 ISO-certified, while Rwanda and Burundi are working toward 9001:2015 ISO certification. It is also important to recognise the achievement made by Kenya, Uganda and Zanzibar considering there was no QMS at baseline. PTF (Rwanda) is moving directly toward the attainment of the ISO 9001:2015 certifications while DPML (Burundi) implemented Quality Objectives and Standard Operating Procedures for some regulatory activities, including Medicines Evaluation and Registration.

Discussion

Harmonization initiatives support regulators' mandate to promote and to protect public health when backed with clear governance structures and regulatory frameworks [46]. The current environment of increased globalization imposed by the geo-economic-political situation warrants advocacy on cooperation and harmonization among NMRAs across the globe [46].

Increased advocacy under the EAC MRH Project has helped in creating awareness on the part of policy makers and politicians on the importance of investing in medical products regulation with subsequent improvement in policy and legal frameworks in all the countries of the EAC region. Implementation of harmonized technical guidelines for registration of medicines, GMP inspection, QMS and IMS has contributed to improved regulatory landscape in the EAC Partner States NMRAs. There has been considerable improvement in the NMRA governance frameworks with subsequent establishment of autonomous agencies. Reliance and attainment of ISO certification by NMRAs are indicators which have attributed to improved efficiency of regulatory processes with resultant increase in number of dossier applications as exemplified by Kenya-PPB, TMDA and Uganda-NDA. Among others, ISO 9001:2008

certification by NMRAs is one of drivers of a robust medicines regulatory system including the attainment of the WHO-GBT maturity level 3. This has been exemplified by TMDA which was the first in the region to attain ISO certification and also the first in Africa to reach WHO maturity level 3, denoting an agency with “a stable well-functioning and integrated system of oversight for medical products” [47].

Regulatory harmonization facilitates pharmaceutical companies’ submission of a single set of the dossier to several different countries with subsequent reduction of costs [48]. Harmonization processes are also beneficial for public health as they facilitate open-minded technical discussions and the exchange of ideas and experience among regulators of different countries contributes to strengthening the capacity of national authorities to expedite the assessment of priority medicines and to filter out unsafe or substandard products [48]. Sound, efficient, effective and transparent regulatory systems are important for the promotion of investment in pharmaceutical sector and socioeconomic advancement [11].

Although some countries have proven to be faster than others in granting marketing approval of products following the regional review process, many companies are now hesitant to use the joint product assessment procedure until efficiency improvements are made [49]. While it has been reported that the regional procedure is of unexpectedly higher quality standards than national procedures, a common frustration is the time taken to receive the actual marketing authorization especially for smaller, less attractive markets [49]. Improvements are therefore required to the current EAC processes to meet the vision of harmonization.

While the baseline assessment tool focused on the national regulatory system legal framework, marketing authorization and regulatory inspection, the indicators tool developed for this research provided more insight in the interaction between NMRAs through the regional process including implementation of regional harmonised guidelines and the uptake of the outcome of the regional joint review and inspection processes.

Research limitations

Missing data from some countries and arranging meetings with people and getting national consents was a problem were some of the limitations of this study

Conclusion

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

The developed indicators tool serve as basis for evaluation of regulatory harmonization networks on the African continent and beyond. Gaps identified and lessons learnt from using indicators tool for this research can be used as basis to refine it for further use.

Abbreviations

ABREMA	Drug and Food Regulatory Authority of Burundi
ACCESS	Drug Registration Software Solutions
AFDRAN	African Drug Regulatory Authorities Network
AMA	African Medicines Agency
AMQF	African Medicines Quality Forum
AMRH	African Medicines Regulatory Harmonization Initiative
API	Active Pharmaceutical Ingredient
AU	African Union
AUC	African Union Commission
AUDA	African Union Development Agency
AVAREF	African Vaccines Regulatory Forum
BMGF	Bill and Melinda Gates Foundation
CIRS	Centre for Innovation in Regulatory Science
CNF	Committee on National Formulary
CTD	Common Technical Document
DPML	Directorate of Pharmacy, Medicines and Laboratory
EAC	East African Community
ECCAS	Economic Community of Central African States
ECOWAS	Economic Community of West Africa States
e-CTD	Electronic Common Technical Document
GDP	Gross Domestic Product
GMP	Good Manufacturing Practice
GRevP	Good Review Practice
GVP	Good pharmacovigilance practice
ICH	International Council on Harmonization of Technical Requiremets for Registration of Pharmaceuticals for Human Use
IGAD	Intergovernmental Authority on Development

ISO	International Standards Organization
IMS	Information Management System
KPPB	Kenya Pharmacy and Poisons Board
LMIC	Low- and Middle-Income Countries
MA	Marketing Authorization
MDGs	Millennium Development Goals
MoH	Ministry of Health
MoU	Memorandum of Understanding
NDA	Uganda National Drug Authority
NDQCL	National Drug Quality Control Laboratory
NEPAD	New Partnership for Africa's Development
NMP	National Medicine Policy
NMRA	National Medicines Regulatory Agencies
NOMCOL	A Network of Official Medicines Quality Control Laboratories
PMPA	Pharmaceutical Manufacturing Plan for Africa
QMS	Quality Management System
RECs	Regional Economic Community
RFDA	Rwanda Food and Drug Authority
RHO	Regional Health Organizations
SADC	Southern African Development Community
SDGs	United Nations Sustainable Development Goals
SIAMED	WHO Model System for Computer-assisted Drug Registration
SoPs	Standard Operating Procedures
SRAs	Stringent Regulatory Authorities
TFDA	Tanzania Food and Drugs Authority
TMDA	Tanzania Medicine and Medical Devices Authority

TGA	Therapeutic Goods Administration of Australia
UHC	Universal Health Coverage
UNECA	United Nations Economic Commission for Africa
USP	United States Pharmacopoeia
WB	World Bank
WHO	World Health Organization
WHO-GBT	World Health Organization Global Benchmarking Tool for evaluation of national regulatory systems
WHO-PQ	World Health Organization Pre-Qualification Programme
Zazibona	Zambia, Zimbabwe, Botswana and Namibia collaborative procedure on registration of medicines
ZFDA	Zanzibar Food and Drugs Agency
ZFDB	Zanzibar Food and Drugs Board

Declarations

Ethics approval and consent to participate

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

Consent for publication

Respondents gave consent to publish results of this study

Availability of data and materials

· All relevant data are within the manuscript and its supporting information files.

· The data collection instruments, and the datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests

Authors have declared that no competing interest exists.

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Author Contributions

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

Authors' information

Not applicable

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Tables

Table 2.1 Indicators Matrix

NO.	INDICATOR TITLE	TYPE	REPORTING LEVEL	FREQUENCY	DATA SOURCES
CATEGORY 1:	POLICY AND LEGAL FRAMEWORK				
Indicator 1:	National Medicines Policy (NMP)	Input	NMRA	Three yearly	WHO NMRA GBT, Government gazette, Ministry of Health
Indicator 2:	Legal framework governing the regulation of medical products	Input	NMRA	Three yearly	WHO NMRA GBT, Government Gazette, National Law, Ministry of Justice library, NMRA records
CATEGORY 2:	NMRA GOVERVANCE				
Indicator 3:	NMRA level of autonomy	Output	NMRA	Three yearly	WHO NMRA GBT, CIRS OpERA programme, Government gazette, NMRA Financial report, Governance structure
Indicator 4:	Availability of structures to support NMRA decision making process	Process	NMRA	Three yearly	NMRA Organisation/governance structure, Medicines law
CATEGORY 3:	NMRA FINANCING				
Indicator 5:	Level of NMRA funding	Input	NMRA	Annually	CIRS OpERA programme, NMRA records, Ministry of Health
Indicator 6:	Reliability of NMRA funding	Input	NMRA	Annually	CIRS OpERA programme, Central Medical Stores records, Ministry of finance records, Approved annual national budget, NMRA records
CATEGORY 4:	MEDICINES EVALUATION AND REGISTRATION, AND GOOD MANUFACTURING PRACTICE (GMP) INSPECTION SYSTEMS				
Indicator 7:	Availability of guidance and procedures for registration of medicines	Process	NMRA	Annually	WHO NMRA GBT, CIRS OpERA programme, NMRA records, Government policies and legislation
Indicator 8:	Availability of a Good Manufacturing Practice (GMP) inspection guidance and procedure	Process	NMRA	Annually	WHO NMRA GBT, NMRA records, Government policies and legislation, WHO Assessment Reports

NO.	INDICATOR TITLE	TYPE	REPORTING LEVEL	FREQUENCY	DATA SOURCES
Indicator 9:	Availability of a process to track product registration applications and timelines	Process	NMRA	Annually	WHO NMRA GBT, CIRS OpERA programme, NMRA records
Indicator 10:	Existence of a regional policy stimulating review timelines	Outcome	Regional	Annually	CIRS OpERA programme, NMRA records
Indicator 11:	Number of products applications with registration decisions per annum	Outcome	Regional	Annually	CIRS OpERA programme, NMRA records
Indicator 12:	Proportion of NMRAs participating in joint assessments	Output	Regional	Annually	CIRS OpERA programme, REC records
Indicator 13:	Proportion of product applications jointly assessed/ reviewed at regional level	Outcome	Regional; continental	Annually	CIRS OpERA programme, REC records
Indicator 14:	Proportion of NMRAs who made decisions within standard time based on regional reports/ assessment/s	Outcome	Regional	Annually	CIRS OpERA programme, NMRA records
Indicator 15:	Proportion of decisions made at country level based on regional report for which a decision was made within standard time	Outcome	Regional	Annually	CIRS OpERA programme, NMRA records
Indicator 16:	Proportion of NMRAs using regionally harmonized guidelines for product registration	Output	Regional	Annually	CIRS OpERA programme, NMRA Records; REC Records
Indicator 17:	Proportion of NMRAs using regionally agreed systems and processes (Joint assessment)	Output	Regional	Annually	CIRS OpERA programme, NMRA; REC Records
Indicator 18:	Joint Good Manufacturing Practice (GMP) inspections conducted regionally	Output	Regional	Annually	REC records
Indicator 19:	Percentage of Good Manufacturing Practice (GMP) inspection decisions made based on document review	Output	Regional	Annually	REC records

NO.	INDICATOR TITLE	TYPE	REPORTING LEVEL	FREQUENCY	DATA SOURCES
CATEGORY 5:	**FUNCTIONAL QUALITY MANAGEMENT SYSTEMS (QMS)**				
Indicator 20:	Implementation of Quality Management System (QMS) requirements by NMRA	Process	NMRA; regional	Annually	CIRS OpERA programme, NMRA QMS Records
Indicator 21:	Percentage of NMRAs ISO 9001: 2015 Certification	Output	NMRA; regional	Annually	NMRAs QMS Records
Indicator 22:	Availability of mechanism for addressing customer concern	Process	NMRA; regional	Annually	WHO NMRA GBT, NMRAs, Customer Complaint Reports, Customer Satisfaction Surveys/Index
CATEGORY 6:	**INFORMATION MANAGEMENT SYSTEMS (IMS)**				
Indicator 23:	Implementation of requirements for an integrated IMS	Output	NMRA; regional	Annually	WHO NMRA GBT, NMRA IMS
CATEGORY 7:	**LEVEL OF TRANSPARENCY**				
Indicator 24:	Availability of key regulatory information to the general public using different platforms	Output	NMRA; regional	Three yearly	WHO NMRA GBT, NMRAs Website, Government Gazette; WHO reports
Indicator 25:	Engagement of stakeholders on different platform(s)	Process	NMRA; regional	Three yearly	NMRA Records, REC Records, NEPAD Agency records

CHAPTER 3

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

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

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

Table 3. 2 Level of NMRA autonomy in the EAC partner states between the years 2011 and 2015.

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

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

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

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

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

Table 3. 4 Medicines Registration System in the EAC Partner States NMRAs; 2011/12 – 2015/16

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

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

Table 3. 5 Different Levels of IMS Implementation by the EAC Partner Sates NMRAs; 2011/12 – 2015/16

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

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

Source: EAC Secretariat MRH Project Progress Report, 2015

Table 3. 6 Information Management System in the East African Community Partner States National Medicines Regulatory Authorities (2016)

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

Table 3. 7 Functional Quality Management System in the EAC Partner States NMRAs; 2011/12 – 2014/15

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

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

Figures

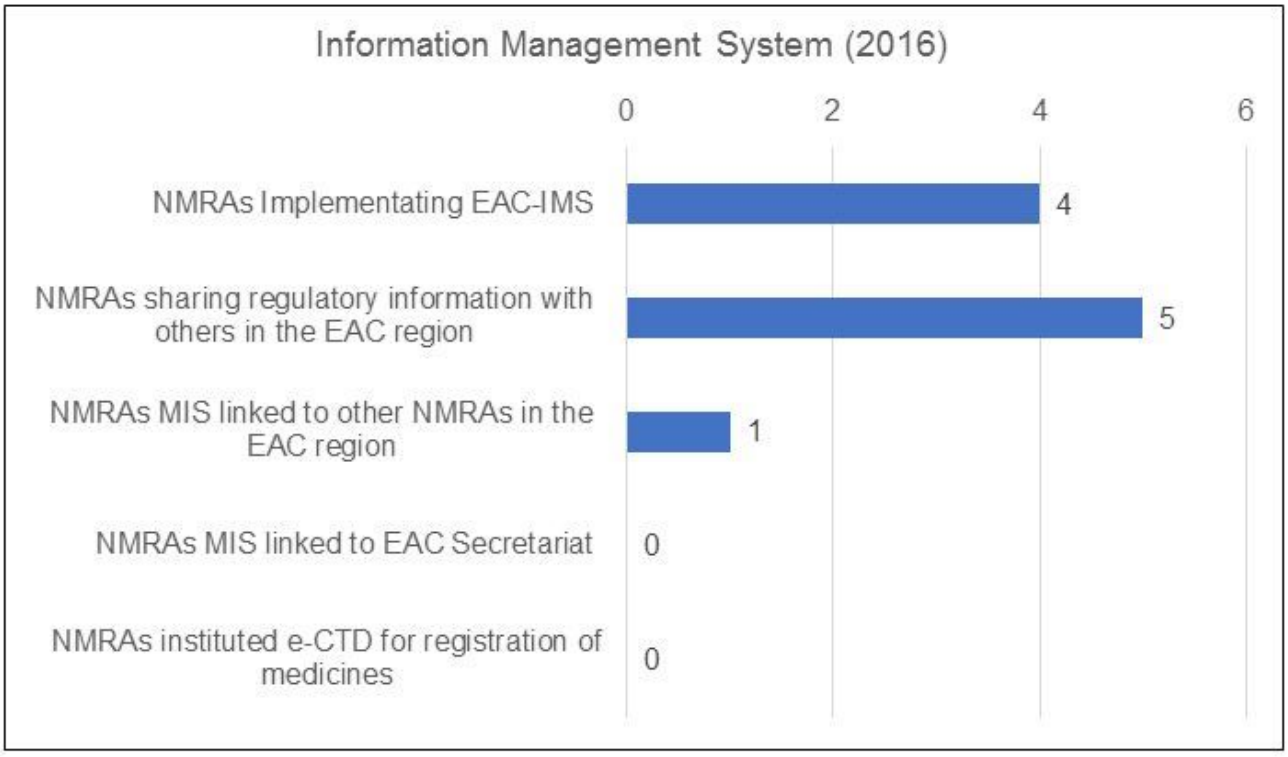

Figure 1

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

Figure 2

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

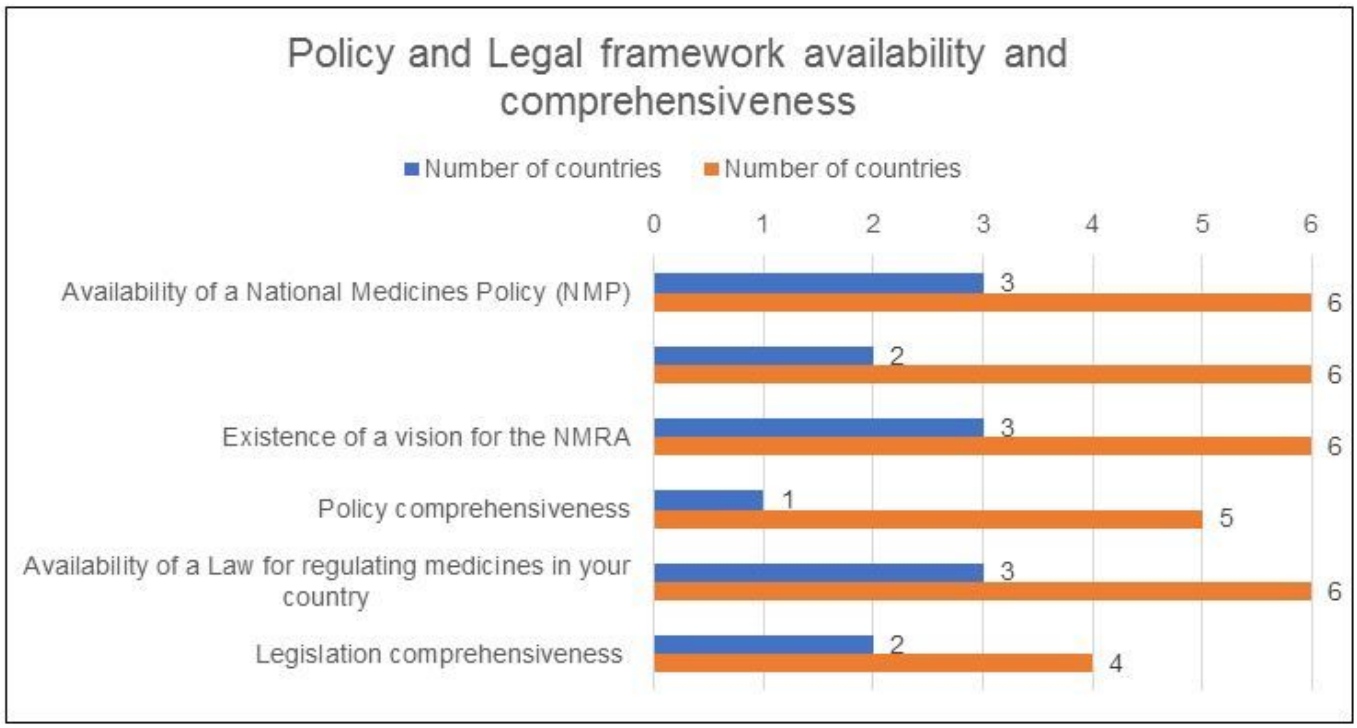

Figure 3

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

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CoverLetterBMCPublicHealth13June2020.doc

- S1QuestionnaireChecklist.pdf