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CURRENT OPINION

Medicines Regulatory Science Expertise in Africa: Workforce Capacity Development and Harmonisation Activities Towards the Establishment of the African Medicines Agency

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Abstract

The medicines regulatory landscape in Africa is undergoing transformation with at least two countries having National Medicines Regulatory Authorities (NRAs) that operate at World Health Organization (WHO) maturity level 3. However, this represents the exception as over 90% of African NRAs have limited capacity to perform core medicine regulatory functions, have a shortage of competent regulatory professionals, have high staff turnover, lack diversity of scientific expertise, and have staffing shortages relative to the high workload. A systematic approach to developing the regulatory workforce is therefore crucial to addressing the existing shortfalls in regulatory capacity, particularly at this time when efforts are underway to operationalise the African Medicines Agency (AMA). In this article, initiatives that are building African NRAs' regulatory capacity and developing their workforce are reviewed in preparation for work to be conducted by the AMA. We found that the African Medicines Regulatory Harmonisation (AMRH) initiative has been at the forefront of capacity building and workforce development mainly through the designation of specialised Regional Centres of Regulatory Excellence and the implementation of medicines regulatory harmonisation initiatives in regional economic communities. In addition, some NRAs within high-income countries and trusted institutions have been supporting regulators in low-income countries with registration assessments and facilitating access to quality-assured medical products through their stringent review procedures (SRPs). Capacity building has subsequently been facilitated through this active involvement of African regulators in SRPs. This article also provides recommendations for further capacity building and workforce development.

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Key Points

Over 90% of National Medicines Regulatory Authorities in Africa have minimal-to-no capacity to undertake medicine regulatory functions that guarantee the quality, safety and efficacy of medical products and they contend with several regulatory workforce challenges.

Formalised in 2009, the African Medicines Regulatory Harmonisation (AMRH) initiative has made significant progress in building capacity and developing the workforce, most notably through the designation of Regional Centres of Regulatory Excellence and the implementation of regulatory harmonisation initiatives in Africa's regional blocs.

The AMRH initiative is proposed to serve as the starting point for the establishment of the African Medicines Agency. However, there is a critical skills gap in Africa in the field of regulatory sciences and an acknowledged need for systematic regulatory workforce development, especially now that the workforce will be required to conduct the work of the continental regulator.

1 Introduction

Regulatory science is "the science that informs, facilitates and/or evaluates regulatory decision making" [1]. It is science applied to medicinal products and focuses on the evaluation of the performance of medicine regulations and regulatory instruments, the development of tools and methods to back regulatory decision making, and the generation of evidence that informs regulatory decisions [1]. Although a specialised field that advances public health and ensures sustainable drug innovation, regulatory science faces challenges due to inflexible recruitment processes, an absence of career structure, job descriptions that do not sufficiently detail the required competencies for positions, incoherent or impromptu regulatory workforce trainings, lack of incentives, and a brain drain [2, 3]. There are also limited opportunities for training in regulatory science in Africa as evidenced by the few academic institutions that provide postgraduate regulatory science programmes and the human resource supply from such programmes is inadequate [2, 4, 5].

The regulatory landscape in Africa is undergoing commendable transformation with countries such as Tanzania and Ghana having an NRA that operates at WHO maturity level 3 for medicines and vaccines as importing countries [6]. However, there are a number of healthcare-related challenges on the continent, which include a high and disproportionate burden of disease, insufficient access to safe, quality-assured, efficacious and affordable medical products, as well as the circulation of substandard and falsified medical products [7–10]. At the national level, there are weak or absent medicines regulatory systems, characterised by unclear policies as well as incomplete or incoherent legal/regulatory frameworks [11]. Although an NRA or an administrative unit performing some or all expected NRA functions exists in all African countries (with the exception of Sahrawi Republic), only 7% of NRAs in Africa have moderately developed capacity to undertake medicine regulatory functions and over 90% have minimal-to-no capacity [11]. African NRAs are reported to lack competent regulatory professionals, have high staff turnover, inadequate staffing numbers relative to the high workload, low diversity of scientific expertise, perennial backlogs, limited financial resources, poor regulatory infrastructure and they face challenges when they attempt to collaborate with other NRAs in the region [4, 5, 8, 9, 12–23].

African NRAs also have lengthy review timelines and most face challenges in meeting regulatory best practices as defined by stringent regulatory authorities [5]. Due to the lack of or limited expertise to perform preclinical and clinical assessments, there are challenges faced in conducting full independent reviews or reliance on NRAs that have different populations and contexts [5]. This presents NRAs in Africa with the difficult task of performing benefit-risk assessments using incomplete safety and efficacy data in the African population [5]. The limited staff in some African NRAs also perform multiple roles and one reviewer can be responsible for the review of quality, pre-clinical and clinical data [5, 24].

A considerable number of agencies in Africa have to raise funds or find partners to support training programmes as well as to attract and/or retain competent personnel [5]. This is due to some of these NRAs not generating income internally that can be allocated to capacity strengthening activities [5]. Additionally, the skills and expertise in clinical pharmacology and regulatory sciences that are available on the African continent are underutilised, partly due to the low presence of research-based pharmaceutical industries, resulting in this talent emigrating to other continents [5]. There is also an increase in the development, manufacture and use of new biotechnological products, advances in medical device technology and an ever-changing digital health landscape, all of which present challenges for regulators [5]. Against this backdrop, systematic regulatory workforce development is considered to be a crucial area to address the shortfalls in regulatory capacity in low resource settings [17].

Therefore, to address national medicines regulatory challenges, the New Partnership for Africa's Development

(NEPAD) Agency, now referred to as the African Union Development Agency NEPAD (AUDA-NEPAD), and key stakeholders formalised the African Medicines Regulatory Harmonisation (AMRH) initiative in 2009 [2, 9, 25]. The aim of the initiative is to create regulatory mechanisms that are more effective, efficient and transparent in various African jurisdictions through collaborative mechanisms, which include joint assessments, joint inspections and reliance that, among others, facilitate shorter timelines for medical product approvals [2, 12, 25, 26]. Good regulatory practices incorporate reliance practices [27]. Reliance refers to a sovereign NRA using the work products of trusted authorities and organisations (e.g. scientific assessments, regulatory decisions) to inform its own decision and perform its regulatory functions [28–32]. Overall, regulatory reliance and harmonisation allow countries to overcome weak regulatory capacity for medicines registration and to reap the public health benefits of having quality-assured, safe and efficacious medical products available on the market in a timelier manner [29]. The AMRH initiative also intends to gradually expand its scope of work, beginning with the registration of generic medicines and moving towards oversight of vaccine clinical trials, pharmacovigilance, and the registration of new chemical entities, medical devices and diagnostics [2, 13, 22].

Additionally, the AMRH initiative, through the Continental Technical Working Group on Regulatory Capacity Development, developed a criteria for establishing Regional Centres of Regulatory Excellence (RCOREs) as part of its mandate to develop and strengthen regulatory capacity in Africa [13, 21]. An RCORE is an institution, or partnership of institutions, with specific expertise in regulatory science as well as proven capacity and capabilities in the training or delivery of services in at least one of the identified categories of regulatory and managerial functions [3, 13]. These institutions include, but are not limited to, NRAs, academic institutions, scientific and research institutions, information dissemination centres, and pharmacovigilance centres [3].

Currently, the AMRH initiative is proposed to serve as the starting point when establishing the African Medicines Agency (AMA) [4, 7, 13, 21, 33–35]. Ncube et al. [11] have provided a review of the vision, mission and value proposition of the AMA as well as progress and challenges towards its establishment. For the AMA to be established, the AMA treaty, which was unanimously adopted by African Ministers of Health in May 2018 [36], had to be ratified by a minimum of 15 African Union (AU) Member States, which also had to deposit their ratification instruments to the African Union Commission. This has been achieved and the AMA treaty entered into being on 5 November 2021 [37]. The ratification process has been slower than anticipated by its proponents and some countries with more robust regulatory systems are yet to ratify. Some reasons put forward include a lack of political will, limited understanding of the proposed governance structure and role of the Agency as well as differences in legal systems and requirements across African countries [38, 39]. Other concerns that have been voiced include uncertainties around costs, the implications of ratification and what the AMA's establishment means for NRAs [38, 39]. In our opinion, a possible consequence of the relatively low participation on the continent is continued concerns over the AMA's hosting, shape/role and governance structure as the countries that have not yet ratified will not be invited to the first meeting of the Conference of the Party to the AMA Treaty where these major decisions will be made. Efforts are now underway to operationalise the AMA and AU Member States are said to have agreed to dedicate part of the time of their NRA staff for the work of the Agency [4, 40–42]. However, there is a critical skills gap in Africa in the field of regulatory sciences and an acknowledged need to develop a long-term training and professional development strategy for NRA staff [5]. It is worth noting that the need for a systematic approach to training and professional development of the regulatory workforce is not unique to Africa. It has even resulted in the WHO developing an adaptable and flexible draft Global Competency Framework that intends to address the global competencies gap for regulators across the spectrum of regulatory functions [5].

This article therefore aims to review initiatives that are building African NRAs' regulatory capacity and developing their workforce as this will soon be required to conduct the work of the AMA. This article also provides recommendations for further capacity building and workforce development, especially now that the AMA—an agency that intends to ensure all Africans have access to safe, quality-assured, efficacious and affordable medical products, that meet internationally recognised standards, for priority diseases or conditions—is in the pipeline.

2 Regional Centres of Regulatory Excellence

In 2014, the AMRH initiative, through the AUDA-NEPAD, spearheaded the designation of 11 RCOREs that specialise in eight regulatory functions, strengthening the development of regulatory capacity by leveraging existing academic, research and regulatory institutions [2, 3, 13, 16, 25]. These institutions include, but are not limited to, NRAs, academic institutions, scientific and research institutions, information dissemination centres, and pharmacovigilance centres [3]. The designated RCOREs are presented in Table 1 and their aim is to support a regulatory workforce that enhances human and institutional capacity in the following regulatory functions: pharmacovigilance, training in core regulatory functions, quality assurance, quality control, medicine evaluation and registration, clinical trial oversight, and the

Table 1 Designated Regional Centres of Regulatory Excellence in Africa [3, 13, 25]

Area of specialisation	Country	Regional Centre of Regulatory Excellence
Pharmacovigilance	Ghana	University of Ghana Medical School—WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance
	Kenya	Pharmacy and Poisons Board (PPB)
Training in Core Regulatory Functions	Tanzania	St. Luke's Foundation, Tanzania—Kilimanjaro School of Pharmacy
	Nigeria	University of Ibadan, Centre for Drug Discovery, Development and Production
Quality Assurance and Quality Control of Medicines	South Africa	North West University (NWU)—WHO Collaborating Centre for the Quality Assurance of Medicines
	Nigeria	National Agency for Food and Drug Administration and Control (NAFDAC)
Medicines Registration and Evaluation, Quality Assurance/Quality Control and Clinical Trials Oversight	Zimbabwe	Medicines Control Authority of Zimbabwe (MCAZ)
Licensing of Manufacture, Import, Export and Distribution, and the Inspection and Surveillance of Manufacturers, Importers, Wholesalers and Dispensers of Medicine	Uganda	National Drug Authority (NDA)
Clinical Trials Oversight	Burkina Faso	University of Ouagadougou—Direction General de la Pharmacie du Medicament et les Laboratoires
Registration and Evaluation and Clinical Trials Oversight	Ghana	Ghana Food and Drugs Authority
Medicine Evaluation and Registration	Tanzania	School of Pharmacy, Muhimbili University of Health and Allied Sciences (MUHAS); Tanzania Medicines and Medical Devices Authority (TMDA)

licensing, inspection and surveillance of manufacturers and importers [2, 3, 13, 25]. Regional Centres of Regulatory Excellence were developed to make ad hoc regulatory training programmes more efficient and effective and to support AU Member States improve their healthcare delivery, regulatory standards and practices [3, 25]. RCOREs are therefore trendsetters, occupying a pivotal role in the development of competent experts in emerging fields of medicines regulation [3]. Through partnerships between NRAs and academic/research institutions, they are increasing the regulatory workforce in Africa using several approaches that focus on the following critical interventions:

1. Providing academic and technical training in regulatory science relevant to different regulatory functions and managerial aspects;
2. Enhancing skills through hands-on training, twinning arrangements, exchanges and job placements in the pharmaceutical industry;
3. Spearheading operational research, including pilot-testing innovations and interventions to inform best practice; and
4. Promoting and scaling up the activities mentioned above [2, 3, 13, 16, 25].

Regional Centres of Regulatory Excellence play a key role as they contribute towards AU Member States attaining a qualified, competent and experienced regulatory affairs workforce [3]. This improves the assessment of the quality, safety, efficacy and performance of medical products as well as improves their quality assurance and quality control [3]. Having regulatory training programmes for African regulators also increases the number of regulatory experts on the continent [12]. By producing an adequate and trained healthcare workforce to perform these functions, there is potentially a subsequent increase in access to essential medical products on the continent and a reduction in the circulation of substandard and falsified medical products [3]. The knowledge pool created by the RCOREs can also be tapped into by AU Member States, the private sector and organisations to improve technical and professional knowledge in the healthcare workforce, especially now that a continental regulator is in the pipeline.

In 2019, representatives from the AUDA-NEPAD, RCOREs, United States Agency for International Development (USAID), Medicines, Technologies and Pharmaceutical Services (MTaPS), United States Pharmacopoeia, and FHI360 met in Accra, Ghana to review and validate a monitoring and evaluation tool to measure the performance of the 11 RCOREs [43]. However, the findings of these assessments are not yet publicly available. It would be of interest to review these findings and obtain an appreciation of the performance and opportunities and threats of the RCOREs. We have not found any independent evaluations

of the RCOREs' performance, which is a possible weakness of the whole structure.

3 Regional Medicines Regulatory Harmonisation Initiatives

There are eight officially recognised regional economic communities (RECs) in Africa and they are defined as independently formed geographical groupings of countries on the continent that intend to promote the integration of mutual regional interests and processes [35]. The eight RECs include the Arab Maghreb Union (UMA), Common Market for Eastern and Southern Africa (COMESA), Community of Sahel-Saharan States (CEN-SAD), East African Community (EAC), Economic Community of Central African States (ECCAS), Economic Community of West African States (ECOWAS), Intergovernmental Authority on Development (IGAD), and the Southern African Development Community (SADC) [44]. Although at different maturity levels, the EAC, ECCAS, ECOWAS, IGAD and SADC have medicines regulatory harmonisation initiatives in place. In this section, we will draw lessons from the EAC, as it is the first successful regional group of the AMRH initiative [15], and SADC.

3.1 East African Community

One of the benefits of regulatory harmonisation is that it facilitates ongoing capacity building by having assessors engage in peer learning and receiving feedback [9]. This is evident in Africa where regional medicines regulatory harmonisation (MRH) initiatives started with the EAC, which consists of Burundi, Kenya, Rwanda, South Sudan, Tanzania, and Uganda [9, 10, 45, 46]. The EAC MRH initiative was officially launched on 30 March 2012 in Arusha, Tanzania with the goal of improving its citizen's access to quality-assured, safe and efficacious essential medical products for the treatment of conditions that have public health importance [4, 9, 10, 13, 15, 45–47].

When the EAC MRH project started, it relied on a Steering Committee, Technical Working Groups (TWGs), and a Project Coordination team to assist it perform its functions [46]. The Steering Committee was composed of Heads of EAC NRAs, chief pharmacists, the EAC Secretariat, and AMRH initiative partners [46]. Meetings were held twice a year by this committee to approve work plans and budgets, as well as to review and endorse guidelines [46]. In addition, TWGs were capitalised on as they are a model which was already being used successfully by the EAC [46]. Leadership roles were assigned for the initiative based on each NRA's strengths:

- Tanzania would lead the Medicines Evaluation and Registration Working Group as it had the most developed semi-autonomous NRA;
- Kenya would lead the Quality Management Systems Working Group;
- Rwanda would lead the Information Management Systems Working Group; and
- Uganda would lead the GMP Inspections Working Group [46].

This regional initiative also designed a twinning system for capacity building. EAC Member States with less mature regulatory systems were paired with more established NRAs, i.e., Zanzibar's NRA was paired with Kenya's, Burundi's with Tanzania's, and Rwanda's with Uganda's [45, 46]. "Healthy cooperation and friendly competition" between NRAs enables high quality and consistent assessments, as well as ensures that assessors are continuously upskilled [48]. This arrangement allowed more mature NRAs to pass on best practices, expertise and institutional knowledge as NRAs worked together on joint activities such as product evaluations and GMP inspections [45, 46]. Furthermore, the twinned NRAs had the opportunity to build relationships and the confidence to enable staff to comfortably communicate with each other, even outside the framework of joint activities [46]. Staff exchanges were also set up to strengthen these twinning relations and to allow for learning from the operations and standard operating procedures of other regulatory authorities, as well as ways to undertake scientific reviews and regulatory activities [45, 46]. By strengthening the regulatory landscape in the EAC region, there is increased local NRA capacity in the region as well as a reduction in the gaps that exist between the various NRAs [47]. This capacity building is viewed to contribute significantly to the reduction in the learning curve, particularly amongst the less mature NRAs [47]. Figure 1 shows the governance structure of the EAC's medicines regulatory harmonisation initiative and Figure 2 shows the role of external partners in the initiative.

Currently, the EAC's decentralised regulatory system is still emphasising work sharing and has all seven member states providing expertise and leadership in a different regulatory domain [10, 46]. This approach facilitates specialisation, ensures that all member states actively participate in the initiative and leverage the region's limited expertise [10, 46]. The EAC MRH initiative is now implementing its "Roadmap for the Future, 2020–2022," which was approved in 2018 by the EAC's Council of Health Ministers [49]. The Roadmap calls for the appointment of regional technical officers (RTOs) who concentrate solely on the day-to-day management of joint regulatory activities as well as recommend programmatic changes to the EAC MRH initiative's Steering Committee [49]. Therefore, each NRA in the region now has an RTO that

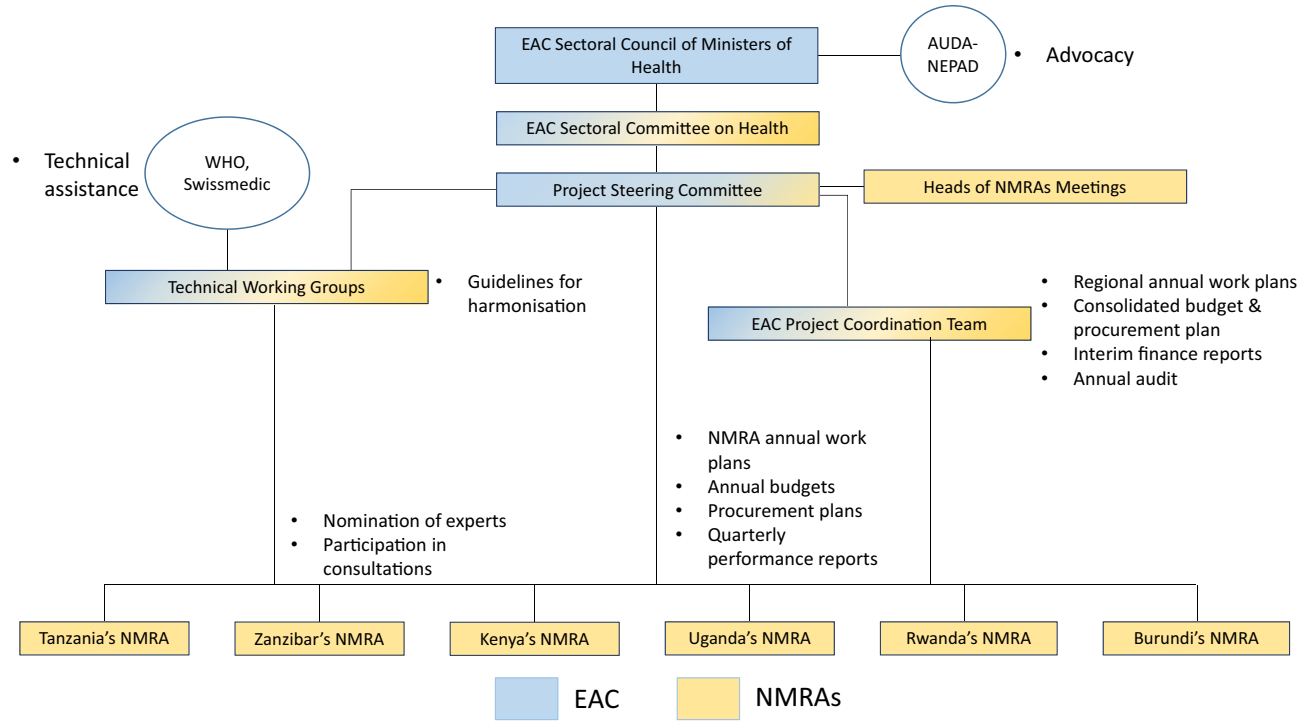

Fig. 1 The governance structure of the EAC's medicines regulatory harmonisation initiative [46]. *AUDA-NEPAD* African Union Development Agency–New Partnership for Africa's Development, *EAC* East African Community, *NMRA* National Medicines Regulatory Authority, *Swissmedic* Swiss Agency for Therapeutic Products, *WHO* World Health Organization

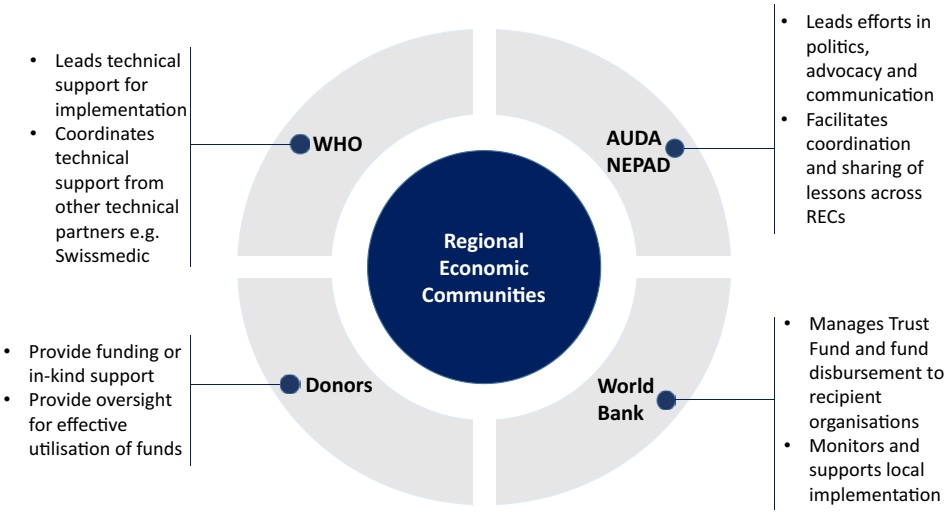

Fig. 2 The role of external partners in the EAC's medicines regulatory harmonisation initiative [46]. *AUDA-NEPAD* African Union Development Agency–New Partnership for Africa's Development, *Swissmedic* Swiss Agency for Therapeutic Products, *WHO* World Health Organization

specialises in a different regulatory domain and serves as the contact point for joint activities. Burundi's RTO supports the oversight of clinical trials; Kenya, pharmacovigilance; Rwanda, information management systems; South Sudan, policy, legal, and regulatory reforms; Tanzania, joint product assessments; Uganda, joint GMP inspections; and Zanzibar, quality management systems [49]. Furthermore, as South Sudan joined the EAC in 2016, the Roadmap has a comprehensive strategy to fully integrate it into the regional MRH initiative and Tanzania's NRA has been working with South Sudan's new NRA to expedite capacity building and the establishment of an effective regulatory system [49].

3.2 Southern African Development Community

The Southern African Development Community (SADC) presents another example of regulatory harmonisation as a mechanism for workforce development. SADC is a REC made up of 16 member states: Angola, Botswana, Comoros Islands, the Democratic Republic of Congo, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, the Kingdom of Eswatini, Tanzania, Zambia, and Zimbabwe [24, 35, 50, 51]. With the technical support of the WHO Prequalification Team, the ZaZiBoNa collaborative medicines registration initiative was established in 2013 by four countries: Zambia, Zimbabwe, Botswana and Namibia [2, 4, 13, 24, 25, 51].

ZaZiBoNa was established to facilitate the availability of quality-assured medical products through work sharing in product assessments, manufacturing site inspections and testing facilities [13]. It was also established to address shared challenges such as significant product application backlogs, high staff turnover, lengthy registration timelines, insufficient financial resources, and limited regulatory capacity, especially for products such as biologics and biosimilars [51]. In 2015, ZaZiBoNa was formally endorsed and officially adopted by SADC Ministers of Health as part of the broader SADC Framework for Regulatory Harmonisation [13, 24, 25, 51]. Since then, the initiative has expanded and now includes 14 of 16 SADC Member States participating either as active members or non-active members [13, 24, 51]. The membership status is based on internal capacity to carry out assessments and Good Manufacturing Practice (GMP) inspections [24, 51]. Lesotho and Mauritius, the remaining two countries, participate in the initiative as observers [24]. Figure 3 illustrates the organisational structure of ZaZiBoNa.

ZaZiBoNa provides a platform for the regulation of medical products and capacity building [52]. Like the EAC MRH initiative, it matched inexperienced regulators with experienced regulators to conduct joint inspections, ultimately contributing to the achievement of AMRH initiative objectives and developing the regulatory workforce [52]. In addition, the MCAZ, which serves as the SADC MRH implementing agency [51], and an RCORE for Medicines Registration and Evaluation, Quality Assurance/Quality Control and Clinical Trials Oversight offers a 2-year fellowship in regulatory science for African medicine reviewers/assessors in partnership with the European and Developing Countries Clinical Trials Partnership (EDCTP) from 2019 to 2022. The regulatory science fellowship aims to support the development of institutional capacity and the capacity of assessors to enable improved regulatory activities directly related to the registration of new medicinal products [53]. The fellowship costs approximately US$28,950 per fellow for the entire programme and to date eight fellows received funding [53].

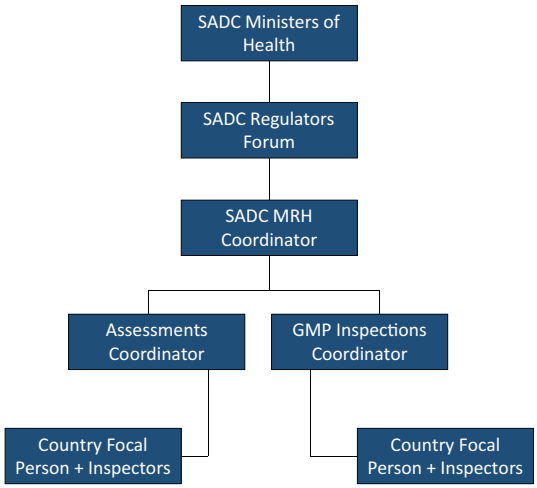

Fig. 3 The organisational structure of ZaZiBoNa, SADC's collaborative medicines registration initiative [51]. This structure provides an enabling environment for capacity development as it holds assessment sessions quarterly on a rotational basis where SADC, World Health Organization (WHO) prequalification, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), and European Medicines Agency (EMA) guidelines are used [51]. This allows for knowledge exchange and creates a platform for participating personnel to acquire practical and hands-on experience through peer learning and feedback [51]. In addition, the assessments coordinator assigns one country (the rapporteur) the responsibility to perform the first review and a second country (the co-rapporteur) performs the second review of the product. The rapporteur and co-rapporteur's final reports are then checked by the WHO as part of quality assurance which provides another learning opportunity [51]. For the GMP assessments, development partners support capacity building for participating ZaZiBoNa countries and each site-inspecting team is usually made up of a lead inspector, co-inspector and observer from different countries, with the lead and co-inspector roles being assigned on a rotational basis among the participating countries that have competent GMP inspectors [51]. *GMP* Good Manufacturing Practice, *MRH* Medicines Regulatory Harmonisation, *SADC* Southern African Development Community

3.3 Workforce Related Challenges Faced by African Regulatory Authorities and Harmonisation Initiatives

Despite the progress made in regional regulatory harmonisation, there are still challenges faced related to capacity and the workforce. In the EAC, the harmonisation initiative reports having a high staff turnover and challenges with understaffing, including in key leadership roles and at the technical staff level. For example, since the initiative began, Burundi trained four pharmacists to perform product assessments and they all left the NRA to join other missions, ministerial departments, international non-governmental

organisations, or the private sector [45]. SADC also reports challenges, which include long registration review times due to an increasing number of applications, considerable backlogs, inadequate number of assessors, a lack of sufficient financial resources, and a lack of competency to assess certain types of product dossiers, e.g., for biologics and biosimilars [51]. Moreover, due to overwhelmed resources, SADC countries with higher workloads have no targets for scientific assessments or for the overall approval process [24].

Many low- and middle-income countries (LMICs) cannot finance their public health needs and their NRAs are particularly vulnerable [28]. African NRAs have relatively small annual budgets, and a significant amount of the budget is earmarked for operational costs. This leaves a relatively small amount for salaries and infrastructure development [54]. According to studies conducted by Ndomondo-Sigonda et al. [54] in the EAC region and Sithole et al. [24] in the SADC region, African NRAs use different financing models, as shown in Table 2. Generally, they obtain funds from their governments, fees for services provided (i.e., fees for registration, annual product maintenance, plant audits, licensing of premises, and import permits) and/or from donors [2, 24, 28, 54].

In some African countries where the NRAs depend on government funding, all fees are paid directly to Treasury [54]. These fees are not redistributed and the funds allocated by the respective governments to their NRAs are not released in a timely manner [54]. While most African NRAs levy fees, they tend to charge arbitrary amounts that are not commensurate with their regulatory workload or value-added activities [28]. This creates a market entry barrier, hinders post-marketing quality surveillance, impedes reliance efforts and prevents potential financial sustainability [28]. Based on these factors, NRAs cannot pay competitive salaries or sustainably finance workforce capacity development activities. Therefore, for effective and long-term functioning of NRAs, goals need to be clearly defined and sustainability (in terms of human and financial resources)

Table 2 Examples of financing models employed by some East African Community and Southern African Development Community Member States

Regional economic community	Member state	Description of sources of funding
East African Community	Burundi	The NRA obtains 100% of its funds from government
	Mainland Tanzania[a]	Industry fees are the main source of funding, contributing up to 73.20% of the NRA's funding. The rest of the funds are obtained from its government and other sources[b]
	Uganda	Industry fees[c] are the main source of funding, contributing up to 98.25% of the NRA's funding
	Zanzibar	Mixed sources of funding; government (50.40%), industry fees (40.60%), and donors and other sources (9%)
Southern African Development Community[d]	Mozambique	The NRA obtains most of its funding from its government and a small percentage comes from other sources
	Namibia	The NRA obtains 100% of its funds from government
	South Africa	Mixed sources of funding; government (70%), and industry fees (30%)
	Zambia	Industry fees (95%) and other sources (5%)
	Zimbabwe	Industry fees (100%)

NRA National Medicines Regulatory Authority

[a]Tanzania is a member of both the East African Community and the Southern African Development Community

[b]There is a high degree of variation in the funds that are obtained from donors. Some NRAs receive donor funding only once over a 5-year duration, while others receive amounts that fluctuate with no remarkable trends [54]. The Bill and Melinda Gates Foundation (BMGF), World Health Organization (WHO), United Nations Industrial Development Organization (UNIDO), Clinton Health Access Initiative (CHAI), United Nations International Children's Fund (UNICEF), Management Sciences for Health (MSH), World Bank, Trademark East Africa Limited (TMEA), German Corporation for International Cooperation (GIZ), Global Fund, the United States Pharmacopoeia (USP) and the United States Agency for International Development (USAID) are the most cited funding partners [54]. Across all NRAs, the overall contribution of funds received from donors was the least among other funding sources [54]

[c]It has been reported that African NRAs set industry fees and charges arbitrarily and they are not necessarily linked to the cost-of-service provision. Resource intensive services are also offered for free [54]. To ensure financial sustainability, there is a need to revise the existing fees and other charges so that they reflect the real cost of service provision [54]

[d]The six SADC countries used as examples show that there is a significant range of fees applied for the review of medical products, depending on their category (e.g. new chemical entities, biologicals or generics) [24]. Namibia charges the lowest fees (US$333) for new chemical entities, while South Africa charges the highest (US$3558). For biologicals, Namibia charges the lowest fees (US$333) while Tanzania charges the highest (US$3500). For generics, Namibia charges the lowest fees (US$333), while Zimbabwe charges the highest (US$2500) [24]. NRAs funded largely or entirely by their governments charge the lowest fees, whilst those that are dependent on industry fees charge higher amounts with the exception of South Africa which receives about 70% of its budget from its government, but charges fees comparable to the NRAs of Tanzania, Zambia, and Zimbabwe, which are funded largely through fees [24]. None of the NRAs charge fees for scientific advice given to applicants [24]

must be institutionalised [28]. NRAs also need to be granted financial autonomy through clear government policies and legal frameworks that allow them to collect and use fees for services rendered [28, 54]. Furthermore, NRAs must develop a fee structure that is commensurate with its regulatory workload [28, 54]. Fortunately, African countries can domesticate the AU Model Law on Medical Products Regulation, which is a non-prescriptive model legislation that assists them to amend, repeal and/or enact laws that grant NRAs the power to levy, collect and use fees for services that they render [28]. Having a financing mechanism that allows NRAs to generate and retain revenue should improve their financial stability, functional efficiency and accountability [28, 54].

Other gaps that have been noted on the continent include inadequate skills to assess active pharmaceutical ingredient master files (APIMFs) and clinical data for novel medical products, biologics and biosimilars [55]. There is also an inability to attract clinical practitioners to provide expertise in assessing clinical data or chemists for active pharmaceutical ingredient (API) assessments [55]. In some instances, there is multiskilling by assessors, i.e., one assessor reviews the entire product dossier, and some assessors have no postgraduate qualifications [55]. Notwithstanding, there are examples in Africa of dedicated pharmaceutical policy and regulatory affairs postgraduate learning programmes such as the University of the Witwatersrand's MSc. (Med) in Pharmaceutical Affairs, the University of the Western Cape's MSc. in Pharmacy Administration and Policy Regulation, and the University of KwaZulu-Natal's MPharm in Pharmacoeconomics and in Pharmacovigilance (on-line). Furthermore, non-profit organisations such as the Fundisa African Academy of Medicines Development promote the teaching of, and provide training in, medicines development in South Africa and other African countries. These are selected examples based on our knowledge and not an exhaustive list.

4 The Contribution of Stringent Review Procedures in Building the Capacity of African Regulators

The registration of medical products by NRAs is a resource-intensive process that requires technical and financial resources that are often lacking in some African countries [56, 57]. NRAs in high-income countries have developed stringent review procedures (SRPs) to support low-income countries in their registration assessments and to facilitate access to quality medicines. The commonly used procedures are the European Medicines Agency EU-M4all procedure, and the Swissmedic procedure for scientific advice and Marketing Authorisation for Global Health Products (MAGHP). In some cases, these SRPs are exclusively for low-income countries, and they all actively involve African regulators, which build their capacity. Under the WHO Prequalification programme, assessors from NRAs in Africa also participate in the assessment processes of the medical products. These initiatives are discussed further below.

4.1 The European Medicines Agency EU-M4all Procedure

In cooperation with the WHO, the European Medicines Agency (EMA) has a mechanism, Article 58 of Regulation (EC) No 726/2004, which may give a scientific opinion for the evaluation of certain medicinal products for human use intended exclusively for markets outside the European Union (EU) [58–60]. Article 58 of the Regulation was established in response to the need for public health protection and promotion as well as to give non-EU countries scientific assistance whilst also facilitating their rapid access to important new medicinal products for the prevention or treatment of diseases of major public health interest [58, 59]. For this purpose, an applicant submits an application to the EMA and its Committee for Medicinal Products for Human Use (CHMP) will, after consulting the WHO, draw up a scientific opinion to the same rigorous standards used for medicines intended for European use [58, 59].

Elements on quality, safety and efficacy of the medicinal product are included in the CHMP scientific opinion assessment as well as a conclusion on the benefit-risk balance of the product and conditions of use based on the intended populations and markets [58]. A public assessment report, similar to the assessment report for centrally authorised medicinal products (EPAR), will then be published within 2 months following the adoption of the scientific opinion under the EU-M4all procedure and it reflects the scientific conclusions reached by the CHMP at the end of the evaluation process. However, commercially confidential information is redacted from the public assessment report [58]. The article 58 procedure is now referred to as the EU-Medicines4all (EU-M4all) procedure as of September 2017 and the intention of this change is to better reflect the global mission to contribute to public health, capacity building and international collaboration [58, 59].

To streamline regulatory activities, the EU-M4all procedure allows regulators from WHO and NRAs in target countries to take part in the scientific advice procedure as expert reviewers of the rapporteurs' assessment reports, providing specific expertise and input including at CHMP or other meetings [58]. However, they have no voting rights at the CHMP [58]. The procedure also provides African NRA staff access to the complete EMA regulatory toolkit, which contributes to their training and capacity building. The EMA regulatory toolkit includes scientific advice, EMA's PRIME (PRIority Medicines)

scheme and accelerated review, where applicable [58]. Additionally, participating in the procedure has allowed African regulators to network with European and WHO experts and thus build their own regulatory capacity [58]. Furthermore, this process builds regional trust in the scientific opinion and ensures the incorporation of local knowledge into the procedure's outcome [61]. Moreover, the EMA provides training and support to maximise the impact of the non-EU regulators involved in this SRP [61]. To date, regulators from Brazil, Burkina Faso, the Democratic Republic of Congo (DRC), Ghana, Kenya, South Africa, Tanzania, and Thailand have participated in at least one EU-M4all opinion [61]. This pathway also enabled these countries to direct their resources to other regulatory functions [61].

In many non-EU countries, the EU-M4all procedure has improved patient access to medicines. We note that six medicines with a current opinion as of April 2019, resulted in 138 regulatory approvals in 90 countries worldwide [61]. Nine countries have given three approvals and four approvals have been granted in the DRC and Kenya. There have been at least 75 registrations on the African continent [61]. The EU-M4all procedure also facilitates registration in target countries and allows for the inclusion of medicines in the WHO Prequalification List through the 'alternative listing procedure' without the WHO Prequalification programme needing to conduct any further review [58, 59]. In addition, innovative medicines may qualify for inclusion in WHO treatment guidelines and/or the Expanded Program on Immunization, depending on the evidence available [58].

In terms of shortcomings of the procedure, Bellaubi et al. [61] report that it has a low number of opinions. In their study that included all procedures with a positive outcome between 2004 and April 2019, they found that 10 positive outcomes had been granted to eight holders and, of these, four opinions were withdrawn by their holders due to changes to treatment guidelines or for commercial reasons [61]. Therefore, there were six medicines with a current opinion as of April 2019 [61]. The EU-M4all procedure has also had limited use due to alternative pathways and incentives that have emerged since its establishment in 2004, e.g., the USFDA has priority review vouchers and considerable fee waivers [62]. Furthermore, many NRAs are reported to be unaware of the procedure or perceive it to be a lower grade review as it does not result in an EU marketing authorisation [58, 60, 62]. However, through a separate application and evaluation of the benefit-risk of the medical product, an approval in the EU can be granted [61]. Moreover, in cases where the scientific opinion generated is accepted, NRAs in target countries take time to assess applications making the procedure no quicker than with other SRA approvals [62].

4.2 Swissmedic Procedure for Scientific Advice and Marketing Authorisation for Global Health Products (MAGHP)

The Bill and Melinda Gates Foundation, the Swiss Federal Department of Foreign Affairs and the Federal Department of Home Affairs signed a Memorandum of Understanding in January 2014, which had the overall goal of accelerating and improving access to high-quality essential medicines and therapeutic products for people living in LMICs [63, 64]. The partnership's intention is to increase the efficiency of the regulatory review and registration process by focusing stakeholders on value-added activities. It also seeks to strengthen the ability of NRAs to protect the health of their citizens through capacity building [63]. Although other regions may be considered to participate, the aim of this joint venture is to support regulators in sub-Saharan Africa and ensure accelerated access to medical products mainly for diseases that affect the region disproportionately [63–66]. This is done through the Swissmedic Marketing Authorisation for Global Health Products (MAGHP) procedure, which is for medicinal products with a known API, medicinal products with a new API, or a new indication for a medicinal product with a known or new API [63, 65].

The MAGHP procedure is the second example of an SRP that is exclusively for low-income countries and actively involves African regulators, which builds their capacity. It performs similarly to the EMA's EU-M4all procedure as it assesses product development packages and applications for marketing authorisation in collaboration with the WHO and NRAs where the product is intended for use [31]. NRAs of the countries concerned actively participate in the MAGHP process and they benefit from being part of the evaluation procedure [63, 64, 66]. By participating, the African NRAs build their own capacities, gain knowledge about the product, establish confidence in Swissmedic's scientific evaluation, and provide their own inputs and comments on the evaluation [63–66]. Inputs and comments may address issues that are country-specific (e.g., climate zone), risk management plans or disease programmes [63]. In addition, as they already have knowledge about the product and access to Swissmedic's assessment and inspection reports, African NRAs are expected to have a shortened authorisation procedure using "well-informed" reliance, and patients can ultimately have essential medicines available faster [63–66]. Regulators from the NRAs of Uganda, Kenya, Tanzania (mainland and Zanzibar), South Sudan, Nigeria, the DRC and Ethiopia have participated in this procedure [66]. Unlike other SRPs, the MAGHP procedure is not limited to specific indications and it results in a marketing authorisation for Switzerland if the product is approved [31, 63, 65]. The role allocation of the parties involved in the MAGHP procedure is presented in Table 3.

Table 3 The role allocation of the parties involved in the Swissmedic MAGHP procedure [63]

Party involved	Activity
Swissmedic	Swissmedic is the leading party for the evaluation of the application and is responsible for timelines, LoQ and Decision sent by day 330. In the case of an approval, the procedure always results in a Swiss authorisation
WHO	WHO facilitates the first contact, in particular, between Swissmedic and the target NRAs. If indicated, WHO experts (e.g., on disease programmes or the Prequalification Team) are consulted to provide scientific expertise on programmatic aspects
(Foreign) NRA	The NRA evaluates the dossier submitted by the applicant and Swissmedic's assessment reports (including the LoQ). If possible, the NRA writes an assessment report reflecting the medical need and regulatory requirements in their country. The NRA comments on Swissmedic's assessment reports, benefit-risk evaluations, preliminary decision, SmPC and PIL and adds its own questions to the LoQ. Country specific documents, e.g., risk management plans, are evaluated by the respective NRAs Provided the dossier has been submitted, the NRAs concerned commit to decide on an authorisation within 90 calendar days after completion of the procedure at Swissmedic. If the dossier has not been submitted at the end of the Swissmedic procedure, the decision must be made within 90 calendar days after receipt of the dossier
Applicant	The applicant submits the dossier to Swissmedic and conducts dialogue related to the dossier processing. Specifies the NRAs to be involved and signals the need to include the WHO The dossier is submitted to each individual NRA concerned as early in the process as possible. Modules 2 to 5 must be identical to the version submitted to Swissmedic. During the MAGHP procedure, the applicant has the option of switching to the standard Swissmedic procedures without the involvement of the NRAs concerned

LoQ list of questions, *MAGHP* Swissmedic Procedure for Marketing Authorisation for Global Health Products, *NRA* National Medicines Regulatory Authority, *PIL* patient information leaflet, *SmPC* summary of product characteristics, *WHO* World Health Organization

In addition to contributing to the capacity building of African regulators through its MAGHP procedure, Swissmedic (in collaboration with the WHO) has also been supporting medicines regulatory harmonisation initiatives in Africa since 2017 [67]. The Swiss regulator became the official technical partner of the African Medicines Regulatory Harmonisation Partnership Platform (AMRH-PP) in August 2018. The AMRH-PP is a mechanism for coordinating efforts to effectively group, foster transparency and supervise the different partners and interest groups that support the AMRH initiative [67]. The support that Swissmedic has provided to the AMRH initiative includes contributing to technical guideline development, implementation and maintenance as well as capacity building programmes and activities in the areas of Medicines Evaluation and Registration (MER), GMP, Quality Management Systems (QMS), and Information Management Systems (IMS) [67]. Swissmedic also attends AMRH Steering Committee meetings as an observer and the Agency supports the WHO Benchmarking programme by providing expertise to WHO's mission in sub-Saharan Africa [67].

Swissmedic offers capacity building hands-on training courses for NRAs in LMICs. The Swiss regulator, in partnership with the WHO, developed a comprehensive regulatory training course that is structured as a "peer learning" four-day workshop where participants get a better understanding of and new skills in the development and implementation of regulatory processes and approaches [68]. The workshop covers marketing authorisation, market surveillance/pharmacovigilance, QMS and GMP inspections [68]. For the GMP training workshop, Swissmedic, in collaboration with the WHO and the Swiss Development Cooperation Agency (SDC), supports inspectors from African RECs to attend the workshop and the nominated participants have their costs and travel arrangements covered by the WHO [68]. There is also an opportunity for inspectors from NRAs in LMICs to shadow Swissmedic inspectors during a GMP inspection. This is done at the request of the WHO and it is based on the need in African RECs as well as on the capacity and availability of Swissmedic [68].

4.3 The WHO Medicines Prequalification Programme

One of the major concerns of the WHO is the availability of medicines to the public, which are of good quality and are safe and efficacious. In 2001, the WHO established the medicines prequalification programme in response to the HIV/AIDS pandemic [69]. The main goal of the programme was to guide United Nations agencies and other international organisations to facilitate their knowledge of pharmaceutical manufacturers whose medical products met international quality, safety and efficacy standards [69, 70]. Over the years, and due to its success in increasing access to treatments for HIV/AIDS, the scope of the prequalification programme has expanded to cover additional therapeutic areas, which include malaria and tuberculosis, influenza-specific antiviral medicines, zinc for managing acute diarrhoea and reproductive health products [69]. Vaccines, in vitro diagnostics, vector control products and quality control laboratories are also now being prequalified [71]. Many countries now rely upon WHO medicines prequalification (WHOPQ) listings as a reliance mechanism to facilitate registration of products in their markets through the WHO Collaborative Registration Procedure (CRP) [70].

For HIV/AIDS products, WHOPQ 'competes' with PEPFAR, which relies on the USFDA's tentative approval procedure (tFDA) for its procurement and provides greater market access compared to WHOPQ [72]. The USFDA tentative approval procedure allows medical products that do not have marketing authorisation in the USA to be purchased by PEPFAR and distributed to limited resource settings [72]. WHOPQ has a number of advantages over the tFDA, such as faster approval for variations and API source changes (about 6 months for WHOPQ vs approximately 2 years at USFDA), which enable manufacturers to be competitive after product launch as they rely on continuous process improvements to lower costs [72]. Secondly, WHOPQ has a separate approval for API suppliers which provides pharmaceutical manufacturers with more options and drives economics [72].

WHO medicines prequalification has helped NRAs free up resources as they can rely on dossier and inspection assessments conducted by WHO through the CRP procedure to reach their own regulatory decision [72]. As a result, NRAs have reduced duplication and they can parallel process more applications as well as reduce registration timelines by applying reliance mechanisms [72]. In the immediate- to longer-term, WHOPQ intends to build the capacity of countries to manufacture and regulate quality-assured medicines [71]. In addition to setting norms and standards, developing guidelines and advising member states on matters related to quality assurance of medicines for national and international markets, the WHO also assists countries in building regulatory capacity through networking, training and information sharing. WHO medicines prequalification is a key component of these activities and mandate, and it conducts several activities that assist manufacturers, contract research organisations (CROs), regulators and medicines quality control laboratories (QCLs) to enhance their respective skills and expertise [69, 71].

Having gained rich experience over the past 20 years of conducting prequalification, which has included assessors from NRAs from several African countries, WHOPQ can pass on the expertise to build capacity in the AMA activities. AMA regulators would have opportunities for:

- Participation in assessment sessions for WHO prequalification that take place every 2 months in Copenhagen, Denmark;
- Participation in the annual prequalification assessment training held at UN City in Copenhagen, Denmark;
- Participation in WHO inspections;
- Rotational fellowships at WHO Headquarters in Geneva, Switzerland for assessors/inspectors of LMICs;
- Participation in the assessment processes for medical products during the assessment sessions;
- Participation in hands-on assessment training organised by individual NRAs or by regulatory networks;
- Participation in training workshops on, among other topics, pharmaceutical development, regulatory data requirements, principles and specific requirements relating to WHOPQ, *Good Manufacturing Practices*, *Good Clinical Practices* and/or *Good Laboratory Practices*; and
- Participation in a peer audit system within the network of QCLs who are involved in prequalification. Such peer audits enable the identification of gaps in technical competence and/or activities, and present a platform to actively work towards eliminating them [71, 73, 74].

4.4 The Challenges of Using Stringent Review Procedures

Although SRPs are beneficial and have contributed immensely to ensuring access to medicines for LMICs, some challenges have been identified, e.g., registration fees charged by some Stringent Regulatory Authorities (SRAs) are high [56]. Second, if SRAs require pharmacovigilance programmes at registration, these programmes may not be effective in practice in sub-Saharan Africa as SRAs cannot effectively control pharmacovigilance activities outside their borders [56]. In addition, although NRAs of LMICs are autonomous institutions of sovereign states, SRPs have in the past resulted in questions about Western interference in LMICs. Nevertheless, stronger involvement and collaboration between SRAs and NRAs of LMICs is essential as access to medical products is a global concern [56].

Stringent review procedures may delay access for African patients as NRAs on the continent have to wait for SRAs to make a decision about a medical product, and it also transfers regulatory decision making to regulators who may have less experience in tropical disease products, presentations and epidemiology, and who are not accountable for the safety and needs of African patients [60]. There can also be considerably different benefit-risk conclusions in Africa and the Global North, even when analyses are performed against the same criteria [60]. Moreover, as resources for WHOPQ and PEPFAR may decline in years to come, SRPs for LMICs cannot be guaranteed in the future [56]. Therefore, African countries need to assure responsibilities for medicines quality, and this warrants expedient support for the African Medicines Agency, including capacity building and upskilling the regulatory workforce on the continent.

5 Conclusions and Recommendations

African NRAs face capacity and workforce challenges, which include having a shortage of competent regulatory professionals, high staff turnover and a low diversity of scientific expertise. Therefore, there is a need to

prioritise the improvement of the workforce conditions of service in order to reduce brain drain and to attract those individuals who are already working in the diaspora to return to the continent and contribute to their NRA and the AMA. Additionally, NRAs in Africa, and the AMA once operational, need to diversify their scientific expertise by attracting and retaining staff from fields such as engineering and allied qualitative sciences to work alongside regulatory professionals from pharmacy and the clinical sciences. Currently, a number of initiatives exist that intend to address Africa's regulatory capacity and workforce challenges and this Current Opinion article has reviewed them. We found that the AMRH initiative has been at the forefront of capacity building and workforce development, mainly through the designation of specialised RCOREs and the implementation of medicines regulatory harmonisation initiatives in RECs. Relevant stakeholders are called to raise funds for more regulatory fellowships that focus on RCORE areas of specialisation to be offered on the continent. RCOREs should also develop a common competency framework, harmonised curricula and a regulatory capacity strategy as part of the current capacity development approach. Additionally, we found that regional harmonisation initiatives have been successful at capacity building through peer learning and collaboration as they designed twinning systems that reduce the learning curve for less mature NRAs. Furthermore, this review reports that some stringent review procedures actively involve African regulators resulting in capacity building. We therefore recommend the formalisation of twinned review and exchange programmes to enable African regulators to work alongside reviewers from SRAs. We further recommend that African regulators be involved in the process of developing regulatory guidelines as this is an unexplored avenue to build capacity and expertise. Finally, to demonstrate the value of investments that have been made and to make a case for continued funding and sustainability, all these interventions that focus on capacity development should be independently monitored and evaluated.

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