African medicines regulatory harmonisation initiatives

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Abstract
Due to human, technical, financial and other resource shortages, many National Medicines Regulatory Authorities (NMRAs) in Africa do not have the full capacity to perform all of the core regulatory functions. These shortfalls contribute to poor health outcomes and lower life expectancy throughout the African continent. In response, African regulators and the international community mobilised technical and financial resources to create the African Medicines Regulatory Harmonisation (AMRH) programme. This programme focuses on developing regional regulatory platforms, as opposed to independent country regulatory systems, while simultaneously strengthening capacity building efforts and encouraging harmonisation of regulatory requirements. Various initiatives have been undertaken through the AMRH programme and significant progress has been made during the last few years, notably in the East African Community (EAC). Similar initiatives are now being rolled out in other regions, including West Africa and the Southern African Development Community (SADC). Around 85% of sub-Saharan Africa is engaged in medicines regulatory harmonisation (MRH) initiatives or similar projects at different levels. These initiatives are making significant progress in mobilising the technical and financial resources needed to advance regulatory harmonisation in Africa. However, there is still much work to be done to achieve the African Union's ultimate vision of a single and comprehensive African Medicines Agency by 2018.

Introduction

In many African countries, the lack of harmonised technical requirements and capacity for medicines registration jeopardises timely access to essential medicines.[1,2] Lack of harmonised regulatory regulations in Africa means that registration regulations, timelines, costs and procedures differ across African countries, thereby discouraging manufacturers from pursuing product registrations in certain African markets. Harmonised medicine regulations in Africa could contribute to the achievement of the Millennium Development Goals relating to health (Goals 4, 5, 6 and 8).[3]

The African Union envisions the establishment of a single African Medicines Agency (AMA) by the end of 2018.[4] The AMA is expected to contribute to an enabling environment for the development of the pharmaceutical industry which lead to better coordination between different partners and stakeholders undertaking medicines regulatory strengthening and harmonisation efforts on the continent. The AMA would be built upon the already existing structures of the five Regional Economic Communities (RECs) and Member States that have begun AMRH programmes within the framework of the Pharmaceutical Manufacturing Plan for Africa (PMPA). Medicines regulatory harmonisation (MRH) is a key component of the African Union's PMPA, which was approved by the AU Conference of Ministers of Health in 2007 and which aims to enable African countries to fulfill their national obligations to provide all citizens with safe, quality and efficacious essential medicines.[4,5]

Overview of the AMRH programme

The AMRH programme is a partnership initiative formalised in 2009 and launched throughout the EAC countries in 2012 (Tanzania, Uganda, Kenya, Burundi, Rwanda).[6] This programme was created through a joint initiative of the New Partnership for Africa's Development (NEPAD), the Pan African Parliament (PAP), and the African Union Commission (AUC), in collaboration with the World Health Organization (WHO), the World Bank, the Bill & Melinda Gates Foundation (BMGF), and the UK's Department for International Development (DFID). The strategy of this programme is to develop regional regulatory platforms with harmonised standards (technical requirements/guidelines), joint regional dossier assessments and good manufacturing practice (GMP) inspections, including worksharing and streamlined decision-making processes. Together, the NEPAD Agency (a technical body of the African Union) and the AUC defined and endorsed the regional networks for implementation of the AMRH programme as indicated in Table 1. These networks build on existing RECs.

Since 2014, the NEPAD Agency has spearheaded the designation of eleven Regional Centers of Regulatory Excellence (RCOREs), leveraging existing academic, research and regulatory institutions[7] to strengthen regulatory capacity development. They were developed to streamline ad-hoc regulatory training programmes and to support AU Member States in improving healthcare delivery. The aim of the designated RCOREs is to support a regulatory workforce that enhances human and institutional capacity in the following regulatory functions: Pharmacovigilance; Training in Core Regulatory Functions; Quality Assurance; Quality Control, Medicine Evaluation & Registration; Clinical Trial Oversight; and the Licensing, Inspection & Surveillance of Manufacturers, Importers and Inspections.[7] The RCOREs use multiple approaches that focus on the following

Table 1: Regional economic communities (RECs).

RECs	Community members
EAC	Burundi, Kenya, Rwanda, South Sudan, Uganda and United Republic of Tanzania.
SADC/COMESA	SADC: Angola, Botswana, the Democratic Republic of Congo, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Swaziland, Tanzania, Zambia and Zimbabwe. COMESA: Burundi, Comoros, DRC, Djibouti, Egypt, Eritrea, Kenya, Libya, Madagascar, Rwanda, Sudan, and Uganda.
IGAD	Djibouti, Ethiopia, Eritrea, Kenya, Somalia, the Sudan, South Sudan and Uganda.
ECOWAS (WAHO/ UEMOA)	Benín, Burkina Faso, Cabo Verde, Côte d'Ivoire, Gambia, Ghana, Guinea, Guinea Bissau, Liberia, Mali, Níger, Nigeria, Senegal, Sierra Leone and Togo.
ECCAS/OCEAC	Angola, Burundi, Cameroon, Central African Republic, Chad, Congo, Democratic Republic of the Congo, Equatorial Guinea, Gabon, Rwanda and Sao Tome and Principe.
CEN SAD/AMU	AMU: Algeria, Libya, Mauritania, Morocco, and Tunisia. CEN SAD: Benin, Burkina Faso, Central African Republic, Chad, the Comoros, Côte d'Ivoire, Djibouti, Egypt, Eritrea, the Gambia, Ghana, Guinea-Bissau, Libya, Mali, Mauritania, Morocco, Niger, Nigeria, Senegal, Sierra Leone, Somalia, the Sudan, Togo and Tunisia.

important interventions: provision of academic and technical training in regulatory science applicable to different regulatory functions and managerial aspects; skills enhancement through hands-on training, twinning and exchange; and practical training through job placement in the pharmaceutical industry.

Approximately 85% of Sub-Saharan Africa is engaged in MRH projects, yet the level of progress and support varies across regions, as shown in Table 2.[4] Each MRH project is progressing at a different pace, with some RECs making significant progress while others require more time and attention to achieve AMRH milestones. This paper details the achievements and initiatives of various MRH projects.

MRH initiatives have been implemented in the EAC, ECOWAS and SADC regions, with uneven levels of progress. At a minimum, a framework for harmonisation of regulatory policies and activities has been initiated in all three of these RECs. As it stands, the NEPAD Agency, in collaboration with ECCAS, OCEAC and WHO, has developed a collaborative framework to outline activities and clearly defined roles and responsibilities for partners involved in the implementation of the MRH initiative is this region. In the North or North Eastern Africa region, the MRH project is in consultation stage only. The Member States of this Northern region recently signed the Khartoum Declaration to Call for Action supporting movement toward the implementation of a regional medicines regulatory collaboration and harmonisation programme.[8]

East African Community – MRH project

The AMRH programme selected the EAC as the first region to begin implementation of its regulatory harmonisation plan, and officially launched on 30 March 2012.[9] The programme aimed to implement harmonised technical requirements, information management systems and quality management systems in each EAC Member State and to build regional and national capacity to implement an EAC-MRH programme. The programme was also initiated to create a platform for information sharing and to develop and implement a framework for mutual recognition of regulatory decisions.[8] In September 2014, the EAC-MRH finalised and approved harmonised registration guidelines, the common technical dossier (CTD), GMP and the quality management system (QMS) compendia. These harmonised guidelines were launched in January 2015 and have been used for several national registrations as well as EAC joint dossier assessments.

It is important to note that the EAC does not have a regional medicines regulatory agency with legal mandate for issuing marketing authorisations for medicinal products. In view of this, and within the framework of the EAC-MRH project, medicines are authorised through one of three channels: (1) National Authorisation Procedure, (2) WHO Collaborative Procedure, or (3) EAC Joint Assessment Procedure. Under the National Authorisation Procedure, each EAC Member State has its own procedures for medicine authorisation; however, each uses the EAC harmonised guidelines for registration of medicines. This procedure results in marketing authorisations in EAC Member State(s) where the application was submitted. The WHO Collaborative procedure is a collaboration between the WHO Prequalification of Medicines Programme (WHO/PQP) and interested NMRAs. This procedure can be used for the assessment and accelerated national registration of WHO prequalified pharmaceutical products. Applicants interested in registration in two or more EAC Member States can submit product registration dossiers through the EAC Joint Assessment Procedure. This procedure entails joint assessment of selected medicinal products and joint inspection of their respective manufacturing site(s) by designated assessors.

Figure 1 illustrates the EAC Joint Assessment Procedure. The process begins with the submission of Expression of Interest (EOI) by applicant to the Tanzania Food and Drugs Authority (TFDA) for screening. TFDA serves as the region's lead Medicines Evaluation and Registration (MER) country. The scope and list of products invited under the EOI, is reviewed and decided by the EAC NMRAs. The National Drug Authority of Uganda (NDA) serves as the lead country for evaluation of Good Manufacturing Practice (GMP) and conducts all GMP evaluations under the EAC Joint Assessment Procedure. Registration fees are paid by the applicants to all NMRAs for each country where the applicant intends to register its products. The letter which confirms the final registration outcome is communicated by the respective country-level NMRAs.

The EAC Joint Assessment Procedure has received a total of 32 applications, of which it has evaluated 27, resulting in four product registrations and 23 queried applications.[9] The EAC-MRH committee estimates that the evaluation procedure was completed 30–40% faster than usual at national levels, resulting in significant cost savings and time savings.[9] The EAC-MRH completed joint GMP

Table 2: AMRH progress (November 2016).		
Regional section	US	EU
EAC	Implementation	Launched in March 2012
ECCAS/OCEAC	In progress	Launched in November 2016
SADC	Implementation	Launched in February 2015
North/North Eastern Africa	Preparatory stage	Launched in July 2015

inspections of nine manufacturing facilities between 2015 and 2016.[9]

Despite recording significant progress, more work remains to achieve mutual recognition, which would enable automatic registration in all Member States once the joint dossier and GMP evaluations are completed via the EAC Joint Assessment Procedure. A Cooperation Agreement for NMRAs in the EAC has been drafted, and approval is anticipated in 2017. This co-operative agreement will provide the legal framework for mutual recognition, which would eliminate the national country procedures, ie, payment of different NMRA registration fees and receipt of final registration approval and certificates from each NMRA. The EAC-MRH initiative is also working on expanding its scope to include pharmacovigilance (PV), devices and diagnostics, vaccines, clinical trials oversight, and variations and renewals.

Southern African Development Community – MRH project

Harmonisation efforts in the Southern African Development Community (SADC) region are facilitated by the Southern African Regional Programme Access to Medicines and Diagnostics (SARPAM). SARPAM was initiated as a support programme for the SADC Pharmaceutical Business Plan, through the Department for International Development (DFID-UK) between 2009 and 2014.[10] The programme was designed in consultation with the SADC Secretariat, Member States and other stakeholders who committed to regulatory harmonisation in line with Article 29 of the Protocol on Health, in 1999. SARPAM provides technical and logistical assistance to SADC Member States. Some of the notable achievements of the SARPAM include the development of the SADC Medicines Regulatory Strategic Framework 2015–2020 and the adoption of the International Council for Harmonisation (ICH) CTD format for medicine registration by SADC ministers in November 2013.[8]

Table 3: Top conditions/diseases in SADC with overall priority ranking.	
HIV/AIDS	1
Tuberculosis	2
Malaria	3
Acute respiratory infections	4
Diarrhea	5
Diabetes	6
Pneumonia	7
Cardiovascular	8
Cancer	9
Obstetrics, gastroenteritis and colic	10

The SADC regional registration guidelines have since been updated and aligned to CTD format. SARPAM further supported the ZAZIBONA project, which was initiated in 2013 and established as a collaborative procedure for medicines registrations between four SADC countries, namely Zambia, Zimbabwe, Botswana and Namibia.[8] In 2014, the ZAZIBONA approach was officially adopted as part of the broader SADC Framework for Regulatory Harmonisation. South Africa and Swaziland (non-active status) officially joined the ZAZIBONA scheme in 2016.

The standard guideline to register medicines via the ZAZIBONA collaborative was published and implemented in June 2015. Any medicine meeting the criteria of being an essential medicine is invited to submit for registration via the ZAZIBONA collaborative process. However, given the SADC focus on ten priority disease conditions (see Table 3) and on reproductive health, special consideration may be given to medicines that are vital to effective treatment of these conditions and to expanding treatment programmes. Priority is also given to the products included in the List of UN Commission for Life-Saving Commodities for Women and Children.

The ZAZIBONA collaboration does not replace the need to submit applications for registration in participating countries in line with national requirements. However, it provides an accelerated application for manufacturers of essential medicines to obtain marketing authorisation in two or more countries participating in this scheme. Figure 2 shows the ZAZIBONA process design. It is important to note that the invited generic products exclude those which have been WHO prequalified and/or registered by Stringent Regulatory Authorities (SRA); other accelerated registration mechanisms can be used for such products. Innovator products which have not been registered by SRAs are accepted for the ZAZIBONA collaborative procedure. Manufacturers based in the six countries involved in the collaboration are also encouraged to apply.

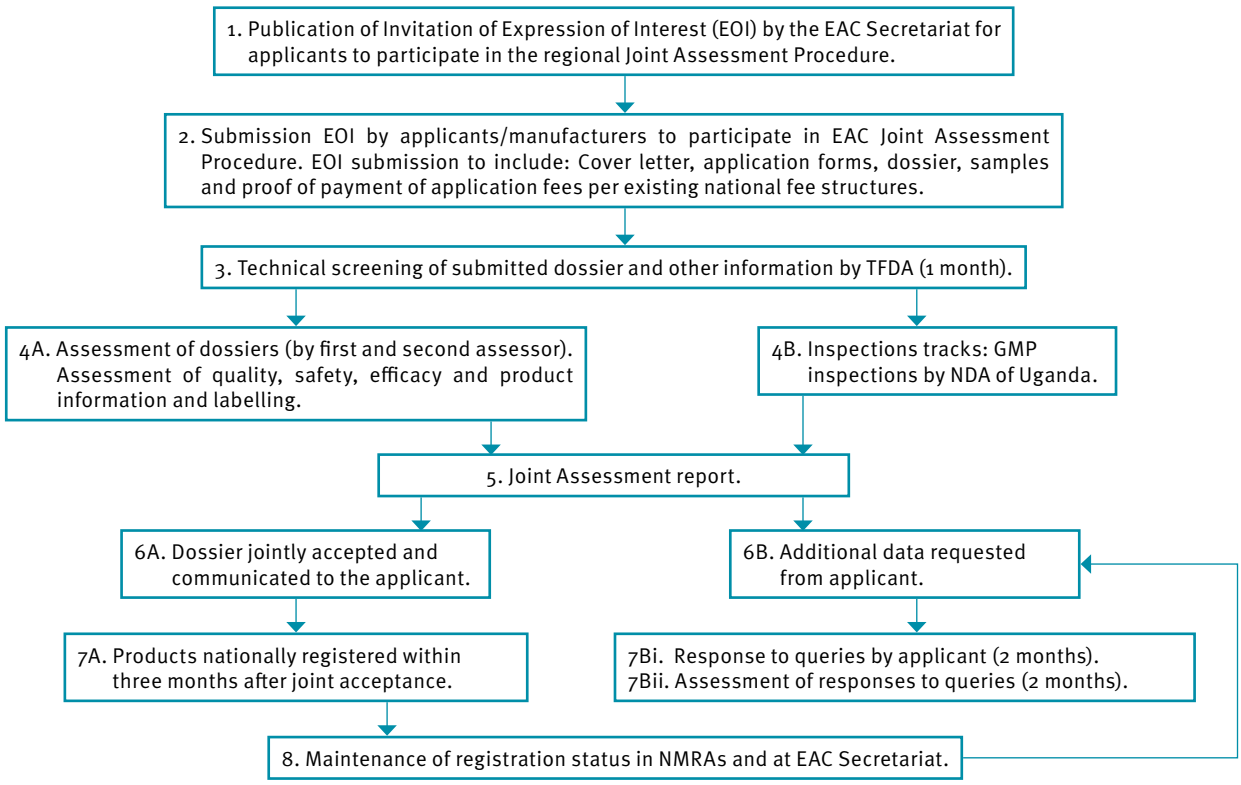
The ZAZIBONA initiative has evaluated 154 product applications over 13 meetings from October 2013 to November 2016. Of these 154 product evaluations, a final decision has been reached for 90 products (56% approved, 33% rejected and 11% withdrawn).[11] The remaining 64 products were queried, and the mean time to recommendation is estimated at nine months.[11]

ECOWAS – MRH project

The MRH programme in the West African region was launched in 2015 in Accra, Ghana.[8] The NEPAD Agency, together with the AMRH partners, facilitated the programme launch, which included the establishment of a joint MRH Programme Steering Committee and formation of seven technical working groups (TWGs).[12] The steering committee managed to align the CTD requirements for the West African Health Organization (WAHO) and the West African Economic and Monetary Union (UEMOA) with technical support from WHO.

WAHO has been provided support to the Economic Community of West African States (ECOWAS) since 2009, when a five-year plan was

Figure 1: EAC Joint Assessment Procedure.



implemented to strengthen registration harmonisation, regulatory management, quality control of medicines, pharmaceutical production, current GMP (cGMP) and pharmacovigilance across the region. UEMOA is the organisation representing the francophone West African countries. Additionally, WAHO and WAEMU have an established collaboration framework and a joint three-year plan of action (2014–2016) for implementation of the MRH programme in this region.[8] Through the TWGs, the region will now begin developing technical guidelines. A series of collaborative activities between regional agencies has also been undertaken as part of capacity and confidence building among the NMRAs.[12]

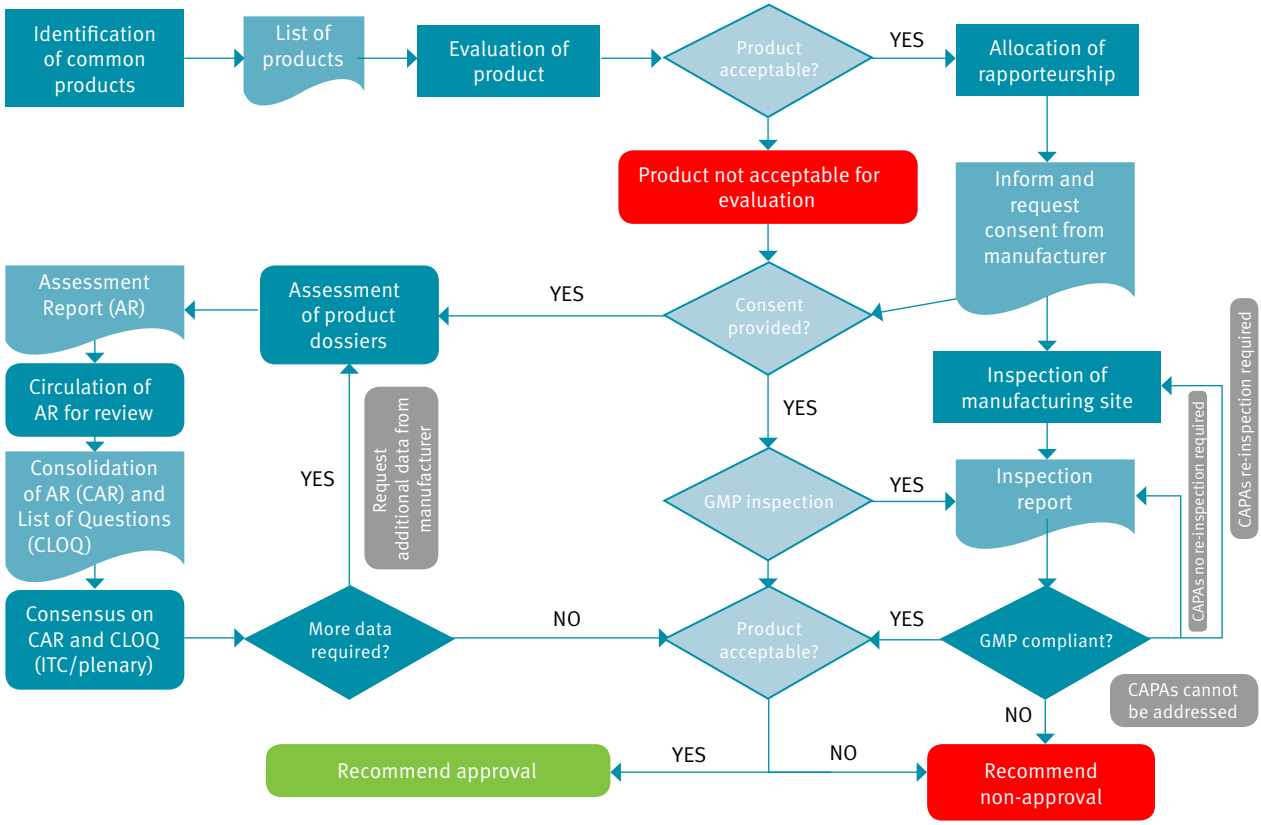
Other MRH projects

- **North/Northeastern Africa.** The consultations regarding AMRH in North/Northeastern Africa began in December 2010 in the Intergovernmental Authority on Development (IGAD) region.[12] In April 2016, the IGAD Member States signed the Khartoum Declaration to Call for Action towards the implementation of a regional medicines regulatory collaboration and harmonisation programme. This took place during the 2nd IGAD Regional Medicine Regulatory Authorities Conference on Regulatory Collaboration and Harmonisation held in Khartoum. One of the recommendations of the Khartoum Declaration was to strengthen NMRAs with inadequate regulatory systems, as well as to strengthen partnerships between IGAD Member States to ensure regulatory harmonisation.[4]
- **Central Africa.** In 2013, the Heads of State of the Economic and Monetary Community of Central Africa (CEMAC) Member States adopted the Common Pharmaceutical Policy (CPP).[12] The Organisation for the Fight Against Endemic Diseases in Central Africa (OCEAC) is responsible for the coordination of health programmes in the region. To initiate activities in the Central Africa region, the NEPAD Agency, in collaboration with ECCAS, OCEAC and WHO, developed a collaborative framework to spell out activities with clear roles and responsibilities for partners involved in the implementation of the AMRH programme. A mapping exercise was carried out in 2016 to establish the status of regulatory systems in Member States. This will help inform the AMRH project development process. A Steering Committee for the implementation of the MRH Project in the CEMAC was launched in November 2016 to provide oversight in the implementation of joint activities. This committee will serve as an entry point for implementation of the MRH Project in the Economic Community of Central African States (ECCAS).

Conclusion

In recognition of the obstacles in the field of medicines registration, the AMRH programme has made significant progress and has mobilised both technical and financial resources to advance the medicines regulatory harmonisation in Africa. The programme has recorded concrete milestones, especially in the EAC and SADC regions, where harmonised regulatory frameworks have been established and implemented. However, more work is required to realise the African Union Vision of establishing a single African Medicines Agency (AMA) by the end of 2018. The establishment of the AMA will build upon the preexisting structures of the RECs and Member States that have already started implementing the AMRH programmes within the framework of the Pharmaceutical Plan for Africa (PMPA). More work

Figure 2: ZAZIBONA Process Design.



is required to drive the AMRH implementation processes in other Regional Economic Communities, such as the North/Northern East Africa and the Central Africa.

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