Pharmaceuticals Policy and Law 18 (2016) 91–98
DOI 10.3233/PPL-160435
IOS Press

Towards African Medicines Regulatory Harmonization: The case of the East African Community

John M. Mwangi
Head, Regulatory Affairs & Quality Assurance Middle Africa, Bayer
E-mail: john.mwangi@bayer.com

The role played by properly functioning regulatory systems towards enhancing access to essential medicines for patients is crucial. This is especially the case in Africa which has seen progressive growth in the regulatory environment. At the center of this growth has been the African Medicines Regulatory Harmonization (AMRH) initiative. This initiative seeks to strengthen regulatory capacity and encourage harmonization of regulatory requirements – with the ultimate aim of expanding access to quality, safe, and effective medicines for patients in need in Africa. A lot of progress has been made during the last years, with initial focus on the East African Community, where harmonization related regulations have already been implemented. The same is now being rolled out in other regions such as West Africa and the Southern African Development Community.

Removing bottlenecks and reducing redundancies in regulatory processes that slow access to medicines for patients in need today is critical. In this sense, collaboration between the World Health Organization and relevant stakeholders, including the research-based pharmaceutical industry, on collaborative registration procedures that support fast and efficient review and approval of essential medicines in Africa is essential.

African regulatory harmonization offers many benefits to regulatory authorities, patients in Africa and industry alike – and most critically for the protection of public health.

Background to the East African Community (EAC) Region

Access to medicines remains a big challenge in the African continent including Anti-Retroviral Therapy coverage among people with advanced Human Immunodeficiency Virus (HIV) infection. Among the many factors that can be attributed to this current situation are the regulatory processes that are required to bring the medicines to patients [1]. The African medicines regulatory environment is as diverse as the number of countries on the continent. There has been general development in the regulatory landscape that is geared towards ensuring availability of safe and efficacious medicines to the populations that require them. With this general progression, often supported by partners such as the World Health Organization (WHO), among others, African countries have set up regulatory systems that are at different stages of maturity [2]. In between has been the realization among stakeholders that these regulatory systems have worked progressively to safeguard the public health of the population. However, they could also become, and have become, to a certain extent a hindrance to the timely access to medicines by the same population they are targeted to support [3]. In particular, diverse requirements developed by individual countries have

increased complexity and decreased the speed of access to the medicines without a commensurate increase in oversight due to the fragmented approach to medicines regulation. It is against this background, that the African Medicines Regulatory Harmonization (AMRH) initiative was launched by the East African Community (EAC) Medicines Regulatory Harmonization (MRH) on 30th March 2012.

The initiative was born out of the earlier pilot projects that had included the WHO joint assessment and WHO Prequalification (PQ) pilot projects of 2010 and 2013. The two WHO PQ pilots, dubbed WHO-EAC joint pilot assessment exercises, were led by WHO with participation of the EAC's national medicines regulatory authorities (NMRAs). In the case of the 2010 pilot, a record registration timeline of seven months was achieved by each of the NMRAs following the joint review exercise [1].

The EAC MRH was launched by the New Partnership for Africa's Development (NEPAD) Agency and the EAC, in collaboration with the AMRH partners WHO, Bill & Melinda Gates Foundation (BMGF), World Bank, the UK Department for International Development (DfID), and the Clinton Health Access Initiative [4]. It had been envisaged that the EAC MRH would be a key contributor towards access to quality, safe and efficacious medicines for priority diseases.

The program was anchored on the already existing EAC regional cooperation on health under Chapter 21 (Article 118) of EAC's treaty on health. The treaty provided for the harmonization of drug registration and regulation with a view of achieving good control of pharmaceutical standards without adversely affecting the movement of pharmaceutical products within the EAC [5]. In 2000, the EAC Council of Ministers, via the Research, Policy and Health Systems Working Group, tasked the EAC Secretariat to draft common drug policy and harmonized regulation and procedures. This policy culminated into the 2005 recommendation to promote regulatory harmonization through existing regional economic communities (RECs), including the EAC, by the African Drug Regulators Conference followed by the 2006 formation of five technical working groups (TWGs). on: administration, quality, good manufacturing practices (GMPs), safety and efficacy, and veterinary medicines. The five TWGs would remain dormant until 2009 when the respective NMRAs under EAC agreed to revitalize with WHO their commitment to support in the funding proposals that led to the launch of the EAC MRH [6,7].

Other partners, such as BMGF, DfID, German Technical Cooperation Agency (GTZ) and NEPAD agency joined WHO in confirming their interest to support the RECs' commitment to promote regulatory harmonization and the funding proposals in May 2009. The project was established with six goals including [5]:

1. Common technical documents (CTDs) for registration to be implemented by at least three EAC partner states;
2. An integrated information management system (IMS) established and linked in all the EAC partner states;
3. A platform for information sharing on harmonized medicines registration system to key stakeholders at national and regional level;

4. Regional and national capacity building to implement medicines registration harmonization;
5. A framework for mutual recognition of regulatory decisions made by other EAC partner states NMRAs; and
6. A quality management system (QMS) to be implemented in each EAC partner states.

In the end, the EAC MRH project was seen by stakeholders and partners to present benefits not only to the NMRAs, but also to the industry. The strengthening of the regulatory landscape in the EAC, as an outcome of the EAC MRH project, has been welcomed by the pharmaceutical industry as this is not only improving the availability of medicines, but also contributing to a well-defined and predictable system that is in line with international best practices such as the use of the CTDs format. Additionally, strengthening of the EAC's regulatory landscape is seen as an effort to increase the local capacity of the EAC's NMRAs and to bridge the gap between the various NMRAs. This capacity building in essence is seen to drastically reduce the learning curve especially among the less advanced NMRAs in the EAC. The lessons learnt from the EAC MRH initiative are crucial to scale up this model to other RECs, as is currently the case in Western Africa with the launch of the West African Health Organization (WAHO)-Economic Community of West African States (ECOWAS) harmonization initiative. Needless to say, the role of other partners, such as the WHO, has helped to ensure that regulatory harmonization is based on existing international best practices and procedures and thereby ensuring compatibility of the new harmonized processes and the NMRA processes with the global pharmaceutical industry practices. The EAC MRH initiative also aims to achieve the most optimal use of resources by encouraging and putting in place processes that facilitate regulatory information sharing, use of risk based approaches, as well as, joint activities. This optimal use of resources will progressively ensure that the already scarce resources at the EAC's NMRAs are put to the best and most value adding activities.

The journey to harmonized regulations

The EAC MRH project was launched in response to the 2010 situational analysis developed by the NEPAD Agency [9]. The report aimed to establish the baseline of the regulatory systems in the EAC member states in view of the projected harmonization initiatives. It made reference to the EAC protocol, which is linked to the harmonization of medicines regulation in the EAC, and highlighted that the legislative regimes of the EAC member states lacked provisions for mutual recognition of regulatory decisions. It also showed that few EAC partner states had clear missions that linked directly to the EAC mission of establishing a common harmonized regulatory system in East Africa. This lack of direction was further exemplified by the fact that the EAC NMRAs were at different stages of achieving regulatory systems set up in the areas of medicines manufacture regulation and registration, distribution,

pharmacy practice and clinical trials regulation. Where registrations processes were in place, the guidelines differed in context, content and format. As regards the approval timelines, the report showed that registrations were taking up to 24 months with six months where fast track procedures were in place for priority disease areas (HIV, malaria and tuberculosis – TB). Regarding human resources, the report showed that there was a deficiency in the capacity and number of personnel working for the NMRAs. The report also demonstrated that the reductions in government funding (especially in those EAC member states where the NMRAs are domiciled within the ministry of health as medicines regulation departments) had a negative impact on the allocation of human resources. Additionally, the report indicated the presence of a pharmaceutical industry and industry associations at different stages of maturity with Kenya as the most developed in East Africa. According to the report, aspects of product registration system were considered to be non-value adding while others were omitted from the process. These redundant processes tended to introduce bottlenecks in the registration process leading to delays in the introduction of medicines in EAC's markets highlighting the need to simplify and standardize regulatory processes.

As a response the NEPAD agency, through the AMRH, started the EAC MRH as the first pilot via the 2011–2015 strategic plan. WHO provided technical support through a memorandum of understanding with the EAC to support the MRH. The project was launched in March 2012 marking the start of the implementation of the AMRH program.

Several partners played a pivotal role within the EAC MRH. In particular, many activities relied on the AMRH trust fund, financed by grants from the World Bank and BMGF among others. WHO was instrumental in helping to establish TWGs, which among other successes, achieved the creation of CTDs.

From early on, the activities amongst the EAC partner states were organized around the TWGs. This was driven by the fact that the EAC secretariat could only coordinate the activities while drawing the real technical input from the NMRAs. Secondly, it helped to begin to bridge the gap between the NMRAs as they began to work together not only to create the guidelines but also to diffuse their expertise across the EAC. This collaboration would in particular become an important aspect towards the mutual recognition stage later on.

The medicines evaluation and registration worked on harmonized registration guidelines structured around the CTD format while the EAC GMPs guidelines and manual were created by the GMPs TWG through a consultative process and under the guidance of the WHO's technical experts. The EAC's QMS requirements and guidelines for implementation of QMS manual were developed by the QMS TWG, while IMS implementation guideline and work plan were developed by the IMS TWG.

Specifically, the medicines registration TWG had the responsibility of developing harmonized technical requirements and guidelines for registration of human

medicines. Additionally, it was assigned to develop assessment guidelines and standard operating procedures for assessment of medicines dossiers and finally identify and develop a list of vital essential and necessary medicines that was to be jointly assessed by the EAC partner states for approval to the steering committee.

During the development of the various working documents and guidelines, the respective NMRAs shared work via face to face meetings and joint working sessions. As an effort to diffuse the knowledge among personnel from the EAC's NMRAs, Zanzibar, Rwanda and Burundi received support to come closer to the level of advancement of Kenya, Uganda and Tanzania. As an outcome, this collaboration between the EAC member states not only contributed to increase the trust among each other, but also to transfer knowhow among NMRAs personnel.

Ultimately, the draft guidelines were reviewed publically by stakeholders including the pharmaceutical industry (both locally and globally) through the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) between 2013 and 2014. This consultation culminated in the endorsement of the guidelines compendium by the EAC Council of Ministers in September 2014 [10]. In January 2015, the EAC Secretariat issued for the first time a call for expression of interest (EOI) to industry for application of new drug application through the EAC Joint Assessment Program [11]. This EOI was limited to priority products for mother and children, medicines for neglected diseases, anti-cancer medicines, and antimalarial, anti-retroviral and anti-TB medicines. Industry responded with several applications which were evaluated jointly with support from WHO and Swissmedic resulting in the recommendation of the first two products for licensing by the EAC partner states. In parallel, the EAC member states started the national harmonization of the medicines registration guidelines: Kenya (July 2015), Tanzania (July 2015), Rwanda (December 2014), Burundi (September 2015), Zanzibar (June 2015), and Uganda (July 2014).

The EAC secretariat established a process for receiving and processing applications as detailed in Fig. 1. The submission is performed to the lead country, Tanzania, followed with screening of the applications within a period of two weeks. This is to be followed by dossiers scheduling on a first come first out basis. The review time is scheduled at 90 days and is provided to have full or abridged evaluation. Upon completion of evaluation the applicant receive registration approval from the respective NMRAs within 90 days. Deficiency Letters responses are allowed for a 60-day period.

Since the launch of the EAC MRH process, a total of 21 products have been submitted. Sixteen out of these 21 products have been evaluated resulting in four registration recommendations out of the first group of eight products, while another set of eight products began the evaluation process in May 2016 with five products currently at the screening stage [12]. Since then, EAC secretariat has issued a second call for EOI which contains an expanded list of eligible products including reproductive health products [13]. It is expected that the success of the first call for EOI will be replicated in this phase.

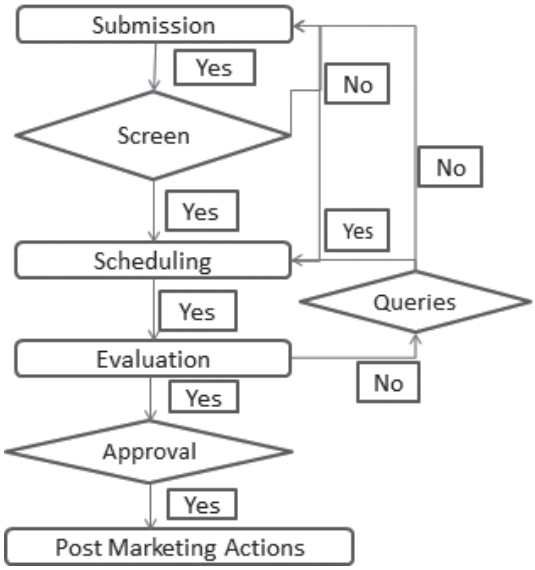

Fig. 1. Submission, evaluation and post marketing process flow for the EAC MRH. Source: EAC Secretariat (http://www.eac.int/).

Additionally, one of the challenges identified by the 2010 NEPAD report referred to a lack of legislation that supports the establishment of regulatory bodies among EAC member states. Since then, the NEPAD Agency, through the AMRH mandate, has led the efforts to develop a model law that guides member states' NMRAs with a base line non-prescriptive law. This law, which was approved by the African Union (AU) Specialized Technical Committee on Justice and Legal Affairs in November 2015, is open for use as a basis for establishing regulatory bodies and supporting legislation in AU member states [14,15]. This model law is expected to provide EAC countries with support in further developing national legislation as necessary.

Role of the pharmaceutical industry in the EAC MRH

The pharmaceutical industry has been a key player and contributor to the development of the EAC MRH through the provision of technical input during the guidelines' production, publication and implementation [16]. The creation of harmonized regulatory guidelines in the EAC has reduced medicines' approval timelines and, as a consequence, decreased the waste of resources (e.g. application of abridged reviews) [12,17] increasing the attractiveness of the African region to the pharmaceutical industry for the introduction of new products with the potential of simultaneous launch. As a result, access to safe, effective and high quality medicines for the treatment of priority diseases has been enhanced.

It is foreseen and expected that the EAC MRH will be extended to develop a framework of mutual recognition of past regulatory decisions by the EAC's member states and achieve full integration of the EAC as a regional health authority. This integration will require a transition from the current joint assessment approach to centralized applications and finally to mutual recognition status [18]. The 2010 NEPAD report stressed that the EAC would continue to act as the benchmark for the rest of the African RECs as Africa works towards the establishment of one regulatory body (i.e. the African Medicines Agency). It is expected that this successful working system will be extended to other regulatory activities such as post market surveillance and variations [19]. As the current guidelines for medicines registration only covers small molecule products, other guidelines will have to be developed to cover biotherapeutic medicines and vaccines.

The handling of GMP certifications should adopt a risk-based approach across the region beyond the current joint inspection approach. This will require the use of desk reviews, recognition of other regulatory bodies' inspection reports, and risk categorization of manufacturing activities. The adoption of the model law should be fast tracked by countries that lack adequate legislation frameworks to establish properly functioning regulatory bodies [2]. In particular, the establishment of the food and drug authority model (as in the United States and Taiwan), distinct and anonymous from the national ministries of health in the EAC member states and with clear funding structures from the national governments, should be effected across the partner states in addition to the establishment of a centralized body at the EAC Secretariat. The financial sustainability of the EAC MRH remains unguaranteed and there is a need to secure it through both national and regional initiatives. The transition clauses need to be defined and anticipated. For instance, the recent announcement of South Sudan joining the EAC economic zone would require foreword looking guidance on how the new country will adopt the already evaluated and approved products through the joint assessments prior to South Sudan joining the EAC. It is imperative that the administrative hurdles that characterize the national systems are eliminated from the EAC procedure especially as more applicants come on board.

Conclusion

The EAC MRH has come a long way from its initial pilot projects. This has taken the efforts of all stakeholders including the pharmaceutical industry and the EAC member states to achieve the current success. It is important to note that despite the challenges that plague the region, the above successes have been accomplished in a relatively short time period. The region should not slow down on this momentum as this approach has demonstrated its potential to significantly increase access to quality and efficacious medicines and, at the same time, positions the EAC region as an attractive region for the pharmaceutical industry to establish their presence. This has

also demonstrated that with adequate coordination and sharing of information as dictated by global trends, it is possible to shorten the learning curve even with regulation of medicines. This implies that the scaling and transfer of these successes to the rest of Africa, namely WAHO and Southern African Development Community (SADC) regions, remains a promising endeavor. EAC should now move to the next stages of lifecycle management regulatory framework (e.g. variations), and regulation of biotherapeutic medicines among others. Establishment of a regional pharmaceutical policy and regulatory framework remains a priority goal of the EAC.

References

[1] S. Azatyan, Overview of African Medicines Registration Harmonization Initiative (AMRH). VII Conference of the Pan American Network on Drug Regulatory Harmonization (PANDRH), Ottawa, Canada, 5–7 September 2013.
[2] WHO Report. Strengthening the capacity for regulation of medical products in the African region. Sixty-third session Brazzaville, Republic of Congo, 2–6 September 2013.
[3] M. Ward, Regulatory Systems Strengthening and Access to Medicines. WHO. 21 May 2015.
[4] WHO support for medicines regulatory harmonization in Africa: focus on East African Community. WHO Drug Information Vol. 28 No. 1, 2014.
[5] Hitti Sillo & Jane Mashingia. Progress of EAC Medicines Registration Harmonization (MRH) Project. San Diego, USA 13 November 2012.
[6] Hitti Sillo. First Joint Product Assessment Experience from EAC Partner States. 14th ICDRA, 28 November-3 December 2010, Singapore.
[7] Apollo, M. EAC partner states' medicines registration harmonization initiative. ICDRA Meeting, Singapore, 28 November 2010.
[8] Owusu-Asante, M. The WHO Prequalification of Medicines Programme Regulatory collaboration. UNFPA/WHO Workshop, Dakar-Senegal, 12–14 February 2014.
[9] NEPAD, 2010. Situation analysis study on medicines registration harmonization in Africa final report for the East African community (EAC).
[10] EAC Secretariat. Press Release. Approval of the EAC medicines regulatory harmonisation guidelines by the 29th meeting of the council of ministers ('the council") held at EAC headquarters, Arusha, Tanzania, 20 September 2014.
[11] EAC Secretariat. Notice to applicants. East African Community's Procedure for marketing authorisation of medicinal products. January 2015.
[12] EAC Secretariat. Overview, Benefits, Opportunities for Pharma Industry and Medicines Authorization Procedure. 21 September 2015, Dar es Salaam, Tanzania.
[13] EAC Secretariat. 2nd Invitation for expression of interest – submission of applications for marketing authorization of medicinal products in the EAC.
[14] NEPAD, 2015. African Union model law on medical products regulation.
[15] PATH Briefing (2016). Increasing access to high-quality, safe health technologies across Africa. African Union Model Law on Medical Products Regulation.
[16] Memorandum of Understanding between the Bill & Melinda Gates Foundation, the Federal Department of Home Affairs and the Federal Department of Foreign Affairs of the Swiss Confederation, 22 January 2014.
[17] K. Narsai, A. Williams and A.K. Mantel-Teeuwisse, Impact of regulatory requirements on medicine registration in African countries – perceptions and experiences of Pharma companies in South Africa, *Southern Med Review* **5**(1) (2012), 31–37.
[18] NEPAD. Conference Recommendations. 2nd Biennial Scientific Conference on Medicines Regulation in Africa. 30 November–1 December 2015. Addis Ababa, Ethiopia.
[19] The AMRH Programme: 2015 Annual Review and Future Outlook. Newsletter, issue 15.