Medicines regulation

Comparison of medicines legislation in the East African Community

Efficient and aligned regulatory systems are crucial in ensuring access to medical products of assured quality. However, marketing authorizations of needed products are often delayed as researchers and manufacturers must navigate multiple regulatory requirements to register their products across countries.

In the East African Community (EAC), efforts are under way for harmonization of technical requirements for medicines regulation. This article presents a comparison of legal and regulatory frameworks for the regulation of medicines in EAC partner states. The findings show some commonalities but also differences and gaps, underlining the need for convergence towards a common medicines regulatory framework in line with international standards.

Background

East African Community

The East African Community (EAC) was established in 1999 among the Republics of Kenya, Uganda, Rwanda, Burundi and the United Republic of Tanzania. With a population of 161.3 million people in 2015 it is home to approximately 14% of the population of the African continent. Life expectancies are below the global average, and all EAC partner states except Kenya are low-income countries according to the World Bank classification (Table 1).

Table 1: Demographic characteristics of EAC partner states

<table>
<thead>
<tr>
<th>Partner state</th>
<th>Land size, km$^2$</th>
<th>Population, million</th>
<th>Gross domestic product (GDP), million US$</th>
<th>Gross national income (GNI) per capita*, US$</th>
<th>Life expectancy at birth**, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenya</td>
<td>569 140</td>
<td>46.1</td>
<td>63 398</td>
<td>1 340</td>
<td>63.4</td>
</tr>
<tr>
<td>Tanzania</td>
<td>855 800</td>
<td>53.5</td>
<td>44 895</td>
<td>910</td>
<td>61.8</td>
</tr>
<tr>
<td>Rwanda</td>
<td>24 670</td>
<td>11.6</td>
<td>8 096</td>
<td>700</td>
<td>66.1</td>
</tr>
<tr>
<td>Uganda</td>
<td>200 520</td>
<td>39.0</td>
<td>26 369</td>
<td>670</td>
<td>62.3</td>
</tr>
<tr>
<td>Burundi</td>
<td>25 680</td>
<td>11.2</td>
<td>3 085</td>
<td>260</td>
<td>59.6</td>
</tr>
</tbody>
</table>

* The World Bank defines low-income economies as those with a GNI per capita of up to US$ 1 025. Lower middle-income economies are those with a GNI per capita of US$ 1 026-4 035.
** Global average 2015: 71.4 years.

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Medicines regulatory harmonization

Harmonization initiatives for regulation of medicines started in 1990 when the medicines regulators and the research-based industry of Europe, Japan and United States of America established the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH, now known as the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use). The objectives of ICH are to improve the efficiency of drug development and registration processes. To date, ICH has published guidelines in all areas of medicines regulation including 12 quality guidelines, 11 safety guidelines, 18 efficacy guidelines and 8 multidisciplinary guidelines (1).

One example of a functioning and successful regional harmonization initiative is that implemented by the European Union (EU), which offers several registration pathways (2). Under the EU centralized procedure, pharmaceutical companies submit a single marketing authorization application to the EMA. The relevant Committee carries out a scientific assessment of the application and gives a recommendation on whether or not to grant a marketing authorization. Once granted by the European Commission, the centralized marketing authorization is valid in all EU member states. Under the decentralized procedure, applications are submitted and subsequently approved simultaneously in several member states, one of which is designated as the “reference member state”. Under the mutual recognition procedure, which is applicable to the majority of conventional medicinal products, already existing national marketing authorizations are recognized by one or more EU member states. National authorizations are still available for medicinal products to be marketed in one EU member state only.

Other regional harmonization initiatives are under way in the Association of the Southeast Asian Nations (ASEAN), the Gulf Cooperation Council (GCC), the Pan American Network for Drug Regulatory Harmonization (PANDRH) and the Southern African Development Community (SADC).

EAC medicines regulation harmonization

Chapter 21, Article 118 of the EAC Treaty (3) provides for co-operation on health and specifically asks partner states to harmonize drug registration procedures so as to achieve good control of pharmaceutical standards without impeding or obstructing the movement of pharmaceutical products, and hence facilitate access to pharmaceutical products within the Community. This is expected to increase access to medicinal products needed to treat health conditions that are prevalent in the region.

The beginnings of harmonization of medicines regulation in the EAC region go back to 2001, when the technical requirements for registration of veterinary drugs were approved by the EAC national medicines regulatory authorities (NMRAs) as exemplified by the Tanzanian guidelines. This was followed by a situation analysis of partner states (4), which highlighted some differences in regulatory capacity and scope of activities as well a lack of institutional mechanisms to share information for example on drug registration or product recalls.

The EAC Medicines Regulation Harmonization (MRH) Programme was launched in March 2012. It was the first programme to receive funding under the African Medicines Regulatory
Harmonization (AMRH) initiative through a trust fund established by an agreement between the Bill & Melinda Gates Foundation and the World Bank. The ultimate goal of the EAC MRH programme is to establish a harmonized regulatory system in the region that enables approval of medicines through various regulatory pathways, similar to the regulation model implemented by the EU Member States.

**EAC medicines regulatory systems**

**Medicines laws**
An overview of the medicines regulatory framework in EAC partner states is shown in Table 2. Some specific aspects are compared below.

**Scope of regulation**
The national medicines regulatory authority (NMRA) of Uganda regulates medicines only, and this includes oversight

<table>
<thead>
<tr>
<th>Partner state</th>
<th>Medicines law</th>
<th>Year of Enactment</th>
<th>Amendments</th>
<th>Regulatory authority</th>
<th>Organizational set-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burundi*</td>
<td>Décret n° 100/150 du 30 septembre 1980 portant Organisation de l’exercice de la Pharmacie au Burundi</td>
<td>1980</td>
<td>None</td>
<td>Department of Pharmacy, Medicines and Laboratory (DPML)</td>
<td>Department under the Ministry of Public Health and the Fight against HIV and AIDS, Head: Director</td>
</tr>
<tr>
<td>Kenya</td>
<td>The Pharmacy and Poisons Act, Chapter 244</td>
<td>1957</td>
<td>2009</td>
<td>Pharmacy and Poisons Board (PPB) <a href="http://www.pharmacyboardkenya.org">www.pharmacyboardkenya.org</a></td>
<td>Statutory body under the Department of Ministry of Health; Head: Registrar and Chief Pharmacist</td>
</tr>
<tr>
<td>Rwanda</td>
<td>Law No. 47/2012 of 14/01/2013 relating to the Regulation and Inspection of Food and Pharmaceutical Products</td>
<td>2013</td>
<td>None</td>
<td>Pharmaceutical Services (Pharmacy Taskforce)</td>
<td>Unit of the Department of Clinical Services in the Ministry of Health; Head: Head of Pharmaceutical Services</td>
</tr>
<tr>
<td>Tanzania</td>
<td>Tanzania Food, Drugs and Cosmetics Act, Cap 219</td>
<td>2003</td>
<td>2004, 2014</td>
<td>Tanzania Food and Drugs Authority (TFDA) <a href="http://www.tfda.or.tz">www.tfda.or.tz</a></td>
<td>Government Executive Agency, Head: Director-General</td>
</tr>
<tr>
<td>(Mainland)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanzania</td>
<td>The Zanzibar Food, Drugs and Cosmetics Act</td>
<td>2006</td>
<td>None</td>
<td>Zanzibar Food and Drugs Board (ZFDB) <a href="http://www.zfdb.go.tz">www.zfdb.go.tz</a></td>
<td>Statutory Board under the Ministry of Health; Head: Registrar</td>
</tr>
<tr>
<td>(Zanzibar)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uganda</td>
<td>The National Drug Policy and Authority Act</td>
<td>1993</td>
<td>None</td>
<td>National Drug Authority (NDA) <a href="http://www.nda.or.ug">www.nda.or.ug</a></td>
<td>Semi-autonomous organization under the Ministry of Health; Head: Executive Director/Registrar</td>
</tr>
</tbody>
</table>

* In Burundi a law relating to regulation of medicines was at the draft stage at the time of writing. This text was obtained from the national medicines regulatory officer and was reviewed for this comparison. No major changes were anticipated until its entry into force. In addition, provisions for medicines registration were published in 2013 in a ministerial order (see Footnote 3 on Page 570 for details).
of the national drug policy and essential medicines list. In Kenya the NMRA also regulates poisons. The NMRAs of Tanzania (Mainland and Zanzibar) regulate food, medical devices, cosmetics and herbal drugs in addition to pharmaceuticals. The law of Rwanda relates to the regulation and inspection of food and pharmaceutical products; however no food regulation is actually carried out. The draft law of Burundi mandates the NMRA to regulate drugs and other products whose consumption can harm health.

Regulation of the pharmacy profession
Regulation of pharmacy professionals – pharmacists, pharmaceutical technicians and pharmacy assistants – is included in the medicines laws of Kenya and Tanzania (Zanzibar). The laws of Uganda, Rwanda, and Tanzania (Mainland) and the draft medicines law of Burundi focus on regulation of medicinal products, while the pharmacy profession is governed by separate laws and is regulated by the professional associations or councils.

Licensing of activities and premises
The laws of Kenya, Uganda, Rwanda and Tanzania (Zanzibar) contain provisions for licensing of retail and wholesale outlets as well as manufacturers of pharmaceuticals. The law of Tanzania (Mainland) covers licensing of manufacturing facilities and wholesale premises engaged in importation and exportation, whereas the regulation of wholesalers and retail outlets is governed by the Pharmacy Act, 2011 with the controls being implemented by the Pharmacy Council. The draft medicines law of Burundi does not include provisions for licensing of activities.

Provisions for registration of medicines
Five of the six medicines laws reviewed include detailed provisions for registration of medicinal products before they are placed on the market. The draft law of Burundi mentions the registration function as part of the Department’s mandate, while details were published in 2013 in a ministerial order.

Provisions for importation of unlicensed medicines in special circumstances are found in the laws of Tanzania (both Mainland and Zanzibar), Kenya and Rwanda and in the 2013 ministerial order of Burundi. The law of Uganda is silent on this issue.

Compliance with good manufacturing practice (GMP)
Kenya, Tanzania (Mainland and Zanzibar) and Uganda have national guidelines on GMP based at a minimum on WHO GMP standards, and compliance with these guidelines is required for medicines registration in these countries. In Uganda, compliance with GMP guidelines is required for licensing of premises under the regulations on Certificate of Suitability of Premises, 2014 of the National Drug

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2 see Footnote 1
4 Available at: http://www.nda.or.ug/files/downloads/Drug%20Certificate%20of%20
Act. The guidelines are detailed and in line with WHO’s current GMP standards, and the NMRA of Uganda is the lead agency on inspections of manufacturing facilities within the framework of EAC-MRH, which signifies the country’s level of strength in this area. The law of Rwanda requires that “pharmaceutical products ... are manufactured in compliance with relevant principles relating to their manufacture” and prohibits manufacture of pharmaceutical products without a license granted under the law; GMP compliance is mentioned in a comprehensive guideline on registration of medicines compiled by the Technical Working Group on Medicines Evaluation and Registration of the EAC MRH Programme, which was approved by the Minister and published on the website of the Ministry of Health of Rwanda in 2014. In Burundi, GMP certificates and GMP inspection are mentioned in the registration application forms, but not in the draft medicines law itself or in the 2013 ministerial order.

Quality control laboratories
In Tanzania (Mainland and Zanzibar) the laboratory is part of the NMRA with appropriate legal provisions. In Kenya there is a legal basis for the quality control laboratory, which is however set up as an independent body corporate with its own organizational structure and management, where the head of the laboratory does not report directly to the head of the NMRA. In Uganda the legal provisions are not explicit but implied and the laboratory is a core department of the NMRA. The quality control laboratories of Kenya, Uganda and Tanzania (Mainland) were the first in the EAC region, and all three are WHO-prequalified. Rwanda has a quality control laboratory under the Rwanda Standards Board under the Ministry of Trade, Industry and EAC Affairs. Burundi has a quality control laboratory under the National Institute of Public Health (INSP), but according to the national strategic plan for laboratory services 2015-2019 it does not currently serve as a national reference laboratory.

Pharmacovigilance
Although the laws of Kenya, Rwanda and Tanzania (Mainland and Zanzibar) mention the follow-up of medicines safety as one of the functions of the regulatory authority, they do not contain specific provisions for pharmacovigilance activities by the regulatory agencies. Nevertheless, in Kenya pharmacovigilance is being executed by the Pharmacy and Poisons Board of Kenya in line with specific guidelines found on the authority’s website, and in Uganda and Tanzania pharmacovigilance activities are also carried out by the respective NMRA. In Tanzania (Zanzibar) medicines safety is monitored by the Zanzibar Food and Drugs Board, while the TFDA is mandated to perform this function throughout the Mainland. The Pharmacy Task Force performs pharmacovigilance in Rwanda, although the medicines law of Rwanda is silent on this issue, as is the draft law of Burundi.

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5 Available at: http://moh.gov.rw/fileadmin/templates/protocols/APPROVED_MOH_GUIDELINES_ON_SUBMISSION_OF_DOCUMENTATION_FOR_REGISTRATION_OF_HUMAN_PHARMACEUTICAL_PRODUCTS.pdf


7 Available at: http://pharmacyboardkenya.org/downloads/?file=national_pv_guidelines.pdf
Control of clinical trials
The laws of Tanzania (Mainland and Zanzibar) describe the approval process for clinical trials and include some provisions for informed consent, trial monitoring and reporting. Related regulations and guidelines are published on the TFDA’s website. Similarly, the law of Kenya mentions the need to conduct clinical trials as a condition for registration of medicines to establish their safety, efficacy or bioequivalence as applicable, while a comprehensive guideline on clinical trials is available on the PPB’s website. The law of Rwanda contains a general statement about the need for imported and domestically produced pharmaceutical products to undergo clinical trials to identify their effectiveness and potential adverse effects related to their use. However detailed provisions could not be found in the public domain either for Rwanda or for Burundi.

Provisions to make specific regulations
The laws of both Tanzania Mainland and Zanzibar enable the Minister of Health, on advice of the regulatory authorities, to make regulations pertaining to products and activities regulated under the respective medicines laws. The laws of Uganda (Section 61) and Kenya (Section 44) provide for making special regulations. The medicines laws of Rwanda and Burundi do not contain provisions to make regulations.

Sanctions
The medicines laws of Burundi and Rwanda do not contain specific provisions for sanctions to individuals or entities that contravene provisions made under the respective laws. The medicines laws of Kenya, Uganda, Tanzania (Mainland and Zanzibar) contain specific provisions for sanctions including monetary penalties, revocation of professional and/or product permits, confiscation of consignments and deportation and imprisonment. The maximum fines under the respective medicines laws are five million Tanzania Shillings (approx. 2 350 US$), 1 million Kenya Shillings (approx. 9 800 US$) and 1 million Uganda Shillings (approx. 300 US$), and the maximum terms of imprisonment are five years in Uganda, two years in Kenya and Tanzania (Mainland), and six months in Tanzania (Zanzibar).

Discussion
NMRAs are entrusted with ensuring the efficacy, safety and quality of medicines, and they are expected to carry out these tasks by applying the best available scientific knowledge and skills without bias. A recent achievement that can support regulatory strengthening and convergence in the region is the publication of the African Union Model Law on Medical Products Regulation (5), which covers the key principles of effective medicines regulation. The review of the medicines laws of EAC countries presented here has identified some differences and gaps that need to be addressed.

Organizational set-up
Good governance including accountability and transparency, sufficient competent human resources to carry out the required tasks, adequate financial resources and freedom from undue influence of politics and the interests of individuals, groups and the public are critical for...
effective medicines regulation. Efficient, independent and unbiased decision-making therefore requires that a sound organizational structure is in place, giving the authority the power to acquire and use resources and to appoint and dismiss staff and determine the level of their remuneration. The AU Model Law recommends that authorities should be autonomous, although they should remain functionally and financially accountable to their Ministries. However, of the six regulatory bodies in EAC partner states only those of Tanzania (Mainland) and Uganda have autonomy in decision-making on staffing and finances. The other NMRAs are Boards or Departments that are dependent on resource allocation from the Ministry of Health, an arrangement that can affect the efficiency of regulatory activities.

Control of activities

Through licensing of activities, NMRAs are able to ensure that medicines are manufactured, stored, distributed and sold in premises complying with regulations and that they comply with the specifications of their marketing authorization until they reach the end users. The NMRAs of Kenya, Uganda and Tanzania (Zanzibar) are in charge of licensing the full range of activities and can institute appropriate measures to safeguard the quality of pharmaceuticals. In Tanzania (Mainland) the responsibilities are divided between the regulatory authority, which controls manufacturing and wholesale (importers’) premises, and the Pharmacy Council, which controls wholesalers and retail outlets. While this arrangement offers clustering of regulatory activities, it may result in loopholes and inefficiency in regulation, as the two parties have different objectives, standards, processes and reporting lines (6).

Pre-marketing control of products

Medicines registration is at the centre of the medicines regulatory functions. It involves the pre-marketing assessment of data submitted by applicants to establish the compliance of products with standards of quality, safety and efficacy. A clear presentation of the technical requirements for registration is important for effective enforcement, as it gives NMRAs the power to refuse registration or to remove products from registers. The laws of Kenya, Tanzania (Mainland and Zanzibar) and Uganda contain detailed provisions for registration of medicines with defined standards to be met in terms of quality, safety and efficacy. In Burundi and Rwanda the law contains a general clause, while detailed provisions were subsequently published in an Order of the Minister. These dispositions enable the EAC countries in principle to control the quality, safety and efficacy of the medicines placed on their markets.

To facilitate convergence of practices a detailed Medicines Evaluation and Registration Compendium was developed under the EAC-MRH programme (7). The compendium is based on the Modules of the ICH Common Technical Document (CTD) format and can be adapted for national use, as has been done in the guidelines published in 2014 in Rwanda.

Currently, Tanzania through TFDA serves as a lead agency in Medicines Evaluation and Registration in the EAC, and so far work-sharing has been successfully demonstrated. Despite the effort made, technical capacity in assessment and registration especially of new chemical entities and biotechnology derived products still poses a challenge towards effective regulation.

Compliance with GMP was found to be a requirement for registration of
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In only three of the six laws reviewed. In the other countries provisions for GMP compliance were in the form of recommendations and guidance and may hence not be legally enforceable. This increases the risk that medicines are assessed and registered even though they are manufactured in facilities that do not comply with GMP. In such facilities there is a higher risk of mix-ups and cross-contamination of products, among other threats, with serious potential impact on the health of patients.

Post-market control of products

Quality control laboratories form an important component in effective regulation of medicines. Their role is to offer pre- and post-registration testing of product samples in order to confirm that a product conforms with its specifications at all times. Functional quality control laboratories are in place in Kenya, Tanzania, Uganda and Rwanda. While in Tanzania and Uganda both functions are under the same roof, in Kenya the laboratory is independent of the NMRA and in Rwanda it is under the Rwanda Standards Board. The latter arrangement facilitates independent analysis and reporting of analytical results without undue influence by findings from dossier assessment and inspections. However, it may affect the efficiency of communication and delay product registration, since pre-registration testing is a requirement for all pharmaceutical products in Kenya.

No quality control laboratory exists in Burundi. Regional collaboration could offer a solution, although cross-border shipment of samples under controlled conditions and communication of results may pose significant logistic and organizational challenges. The absence of quality control laboratories can therefore delay regulatory actions and impact the patients.

Pharmacovigilance is important to detect adverse events observed with medicines on the market. Although pharmacovigilance activities are being carried out in EAC countries, the absence of specific legal provisions in this area is likely to hinder the effective control of safety of registered medicines, as guidelines published by individual partner states may not be legally enforceable.

Control of clinical trials

Effective regulatory control of clinical trials is another important aspect of medicines regulation. For this purpose, laws must contain detailed provisions on how pharmaceutical companies should apply for permission to carry out clinical trials, and how NMRAs in collaboration with Ethics Committees should perform ethical and regulatory review, approve clinical trials, inspect clinical trial sites, and follow-up periodically on the conduct of the trials according to the approved protocols. The full range of the above-mentioned provisions was not found in all the medicines laws reviewed. However, an approval process for clinical trials exists in EAC countries, with detailed regulations and guidelines available in some of the partner states. Cooperation and capacity-building were stepped up when the need for clinical testing was urgent. During

products circulating in countries comply with the specifications of their marketing authorization on an ongoing basis.
the Ebola crisis the African Vaccines Regulatory Forum (AVAREF) served as a common platform for regulators and ethics committee in reviewing and approving clinical trial applications (8).

**Enforcement of legal provisions**
Enforcement of medicines legislation depends to a large extent on the deterrent effect of sanctions. The fines and jail terms specified in the laws of EAC partner states are relatively low compared to the profits often realized by unlawful dealers of medicines, and are in no way commensurate to the risks that substandard and counterfeit medicines pose for the population. By contrast, in a small EU country with 1.4 million inhabitants, Estonia, dealers of medicines who contravene the provisions of the Medicines Act\(^\text{11}\) are liable to pay fines of up to 32 000 Euro (approximately US$ 35 700), and certain offenses are subject to prosecution and punishment under other laws, for example criminal law.

**Adaptation to change**
Provisions to make specific regulations enable governments to accommodate the need for new regulatory functions as they emerge. The AU Model Law on medical products regulation gives the supervisory authority (i.e. the Ministry in charge of health) the power to make regulations and guidelines necessary to pursue the objectives of the medicines law, in consultation with the regulatory authority. Clauses to this effect are included in the laws of Uganda, Kenya and Tanzania (Mainland and Zanzibar). The laws of Rwanda and Burundi are silent on this aspect, and this means that the agencies have to go through the often bureaucratic process of amendment of the main laws every time an update is necessary. The resulting loopholes may encourage acts of unlawful dealing in medicines, especially as the general statutory laws of EAC countries do not have adequate sanctions in place compared to the potential profit to be made by illegal activities.

**Limitations of this comparison**
The comparison presented in this article focused on the medicines laws of EAC partner states. It did not systematically take into account other laws or the full range of regulations that affect the control of medicines. Nevertheless, the findings identify the main gaps and opportunities for achieving effective regulation through harmonization and can thus be useful in improving the legal systems in EAC partner states as part of the ongoing EAC harmonization process.

The review focused on the main regulatory functions. In addition to providing for these, the AU Model Law includes some “Miscellaneous provisions” on management of conflicts of interest, the extent of liability of NMRAs for loss or damage arising from their decisions, and protection of and access to information. These aspects were not considered in this article, although they can have a direct impact on the control of medicines. For example, a review of WHO assessment reports of regulatory systems in African countries (9) found that in many cases medicines regulation is not sufficiently independent from the procurement function, and that there is limited public access to up-to-date registers of authorized products, licenced premises and professionals.

Conclusion

The medicines laws in EAC partner states cover most of the key regulatory functions, and NMRAs are in place. The laws are at different stages of implementation, with some partner states having significantly more regulatory capacity and experience than others. On the other hand, some of the older laws have not been recently reviewed or amended to keep up with the pace of pharmaceutical innovation and technology. Some NMRAs conduct key functions that are not provided for in their respective medicines laws.

Differences were found in the legal provisions for key regulatory functions as well as in regulatory practices of EAC partner states, potentially creating delays in bringing needed medicines to the populations and presenting legal loopholes that can easily be exploited. The sanctions stipulated in the laws are generally not severe enough, nor enforced to a sufficient extent, to deter unlawful dealing in medicines across the EAC region.

The differences and gaps need to be addressed in collaboration, since all EAC partner states are faced with similar health and economic challenges. Future challenges are likely to be experienced across the region as globalization and cross-border trade and travel increase. These developments call for convergence of regulatory practices in the region by streamlining the existing legal and regulatory frameworks towards a common medicines law in the region. The medicines regulatory harmonization programme in EAC partner states is a good start towards achieving this objective.

References