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FINAL REPORT

DEVELOP A SUSTAINABLE FINANCING MODEL FOR THE MEDICINES REGULATORY AGENCIES IN THE EAST AFRICAN COMMUNITY COUNTRIES

August 2016

LION'S HEAD
global partners

Introduction

The East African Community Medicines Regulatory Harmonisation (EAC-MRH) Programme was launched in 2012 with a charitable purpose of improving access to safe, efficacious and good quality essential medicines in the East African Community Partner States. The overall goal of this programme is to have a harmonized and functioning medicines registration and regulation system within the East African Community (EAC) in accordance with the national and internationally recognized standards and best practices.

The ambitions of the harmonisation project are clear: improved regulation of medicines across borders with more streamlined procedures should lead to overall savings in public health budgets. In addition, NRMAs can achieve greater financial sustainability due to reduced duplication and increased demand for registration in the EAC region. Keeping the public health perspective foremost in our minds, the availability of improved products resulting from EAC-MRH will help reduce the burden of disease and drain on national health facility resources. Building out regulatory technical capacity through eliminating replication will contribute to the development of better local pharmaceutical expertise, expanding the role and influence of EAC Medical Research Institutes. Finally, harmonisation alongside effective data management and coordination would also lead to reduced risk of stock-outs and better allocation of inventory by pharma groups throughout the region, through improved market information.

Four years into the harmonisation program, the EAC-MRH remains reliant on donor funding, and all regulatory processes are administered at the national level. The EAC-MRH programme is being collaboratively implemented by all the six National Medicines Regulatory Authorities (NMRAs), overseen and coordinated at a regional level by the East African Community Secretariat. Lion's Head Global Partners (LHGP) has been appointed as a consultant to the EAC and the World Bank in order to address the challenge of financial sustainability in the NMRAs, and to prepare a financial model and accompanying report, as well as a political roadmap for implementation of the recommendations.

Our challenge is to develop a sustainable financial model that enables the EAC system to work more efficiently, but ensures the regulatory agencies remain profitable. This is a challenge being faced by similar initiatives in West Africa, the South African Development Community (SADC) and ultimately across Africa as a whole. The harmonisation process must be driven by member states themselves, and this report and the accompanying financial model are there to support that process, in the strong belief that through harmonisation, the united EAC will be greater than the sum of its member countries. The sustainability and security of financing for regulatory agencies allows for robust and up-to-date policy frameworks, ensuring effective and impactful regulatory review and sufficient oversight for funders and other key institutional stakeholders. The aim of this set of recommendations is to provide a set of solutions around the existing EAC product approval process to ensure NMRA financial sustainability. This report is supported by an earlier report outlining our thinking, methodology and approach.

LHGP attended the 4th Forum of Heads of EAC NMRAs in Entebbe in June 2016, where we presented our preliminary findings to the 8th EAC Regional MRH Steering Committee. Based on this feedback, and an ongoing dialogue with other stakeholders, LHGP developed a set of recommendations and met NMRAs and other partners in person in August 2016 to discuss these. Following these meetings, this report builds on our earlier report to set out recommendations to support financial sustainability in the harmonised EAC. Our earlier report outlined an "ideal" financial model. After further consultation with EAC stakeholders and in particular the EAC NMRAs, we have created a set of recommendations that both reflect the long term vision for the EAC and an associated plan for financial sustainability, as well as transition recommendations that take into account what is politically viable at this juncture. As such, our transition recommendations act as a political roadmap for how NMRAs within the EAC may move towards a united long term vision for regulatory harmonisation in such a way that is politically acceptable today.

In this way, each of the recommendations contained herein have been developed with an understanding not just of what is good, but what is politically viable for the EAC as a whole and the NMRAs individually. We expect that further detail on the next steps for moving forward with implementation of these recommendations will be informed by the reception of the NMRAs as to the findings of this report, and we will be guided by their views on the best way to proceed. Our earlier draft report and some of the recommendations discussed with NMRAs included different recommendations but these have now been updated based on perceived political viability.

Central to our thesis is the idea that genuine harmonisation will lead to an increase in the attractiveness of the East African Community as a target market for international pharmaceutical manufacturers. This will mean an

associated increase in the number of products that manufacturers are looking to bring through the regulatory process. Feedback from pharmaceutical partners supports the premise that the level of drug registrations in East Africa is too low at the current pace – that the volume of distinct new drug applications within the EAC is not static. This is due to a number of factors, including limited commercial market and onerous regulatory processes. The EAC-MRH project means that there is not only a larger commercial market, but also a less burdensome regulatory process. Within the current structure, whereby all applications are administered at the national level, there is needless replication of processes, meaning that following harmonisation, scarce regulatory resources can be better used to complement each other. With the resources currently dedicated to registering the same products in all five EAC markets, the combined EAC region could see many times that number of new therapies reaching their citizens. Additionally, there is a backlog of applications that could be fast tracked.

Our recommendations set out steps that NMRAs within the EAC can take to improve the efficiency of their registration process in order to catalyse this increase in volume. Similarly, they highlight the importance of maintenance (imports and retention fees) as a source of ongoing agency profits, and how NMRAs can leverage this to secure more sustainable sources of financing for ongoing agency activities. Finally, we consider the governance of the EAC, and how the EAC as a region can show leadership in moving towards a regulatory system that is far more targeted and sensitive to the needs to EAC citizens, while setting an example for harmonisation across Africa. Important thing to emphasise in EAC-MRH is that like all voluntary transactions, and unlike many externally-imposed initiatives, EAC-MRH is truly a win-win. In developing these recommendations, an overarching important consideration has been that in none of these recommendations does anybody lose out – true harmonisation will be a win-win for countries, patients, regulatory systems and pharmaceutical companies alike.

This report is grouped around five themes. For each of these, we will look at recommendations for long term sustainability in line with the ultimate goal of full EAC Medicines Regulatory Harmonisation – mutual recognition across all member states – and how that feeds into other harmonisation initiatives across the African continent. The five thematic areas are split into long term vision and transition recommendations, which act as a political roadmap:

1. Increased Efficiency in the Registration Process
2. Maintenance
3. Governance and Capacity
4. Developing East African-Specific Capacity
5. Global Presence and Leadership

Each recommendation is broken down into whether it is applied at the national or regional level; whether it addresses a political or financial challenge; and whether the change recommended is a question of institutional or human resource capacity. These are outlined in the Recommendation Table below.

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Our Recommendations: Summary Table

Recommendation	Description	National Vs. Regional	Political Vs. Financial	Capacity Vs. Structural
Ongoing Capacity and Trust Building Through Joint Activities				
1.1 Fees Remain at Current Levels	Each Agency continuing to charge their designated registration fees.	●		
1.2 Scaled Down Joint Evaluation Sessions	Agencies moving to more scaled down participation in Joint Evaluation sessions.	●	● ●	●
1.3 Scale up Joint Assessment Activity with Opinion Issued	Two NMRAs conducting simultaneous new drug reviews and issuing opinions for national approval.	●	● ●	● ●
1.4 Streamlined GMP Approval Process	Streamlining of GMP inspections by reducing re-inspections, conducting desktop reviews and leveraging expertise of SRAs.	●	●	●
1.5 Expedited Review for those Products Already Registered by SRAs	Avoiding duplication and increasing efficiency of review process by leveraging resources of SRAs.	●	● ●	●
1.6 Increased Mentorship Program to Build Capacity	Institutionalising mentorship and twinning programs to build capacity.	●	● ●	●
1.7 Agencies move towards Unilateral Recognition in Select Areas	Moving towards unilateral recognition within EAC by establishing trust and faith in capacity.	●	●	●
Regulatory Environment Supports Maintenance Revenues				
2.1 Clarity in Guidance around Compliance	Maintaining clarity in guidance and compliance throughout the regulatory process.	● ●		●

2.2 Increased Pharmacovigilance Activities	Focusing on market surveillance and pharmacovigilance activities to increase market transparency.			
2.3 Using Data to Improve Market Attractiveness	Establishing viable commercial market by providing accurate data on healthcare market within EAC and reducing informational barriers for pharmaceutical companies.			
Coordination at the National Level				
3.1 NMRAs take ownership of different areas	NMRAs continuing the existing hosting of responsibilities.			
Remove Barriers to EAC-specific Innovation				
4.1 Waiving requirement for product to be registered in country of origin	Simplifying process for waiving of the requirement for drug review in the country of origin.			
4.2 Products for Joint Evaluation are set by NMRAs	Moving ownership of the EAC harmonisation process away from donors to NMRAs.			
4.3 Fast Track Review can be used to support National strategic health priorities	Using fast track review procedure to support national public health outcomes and maintain national sovereignty.			
Establish Global Leadership and Presence				
5.1 Work with global donors to establish new frontiers in harmonisation	Creating strong health system aligned across borders to rapidly and effectively respond to epidemics.			
5.2 Maintain coordination with other Regional Harmonisation Initiatives	Engaging with regional partnerships and leveraging work done by other regional collaborations to support harmonisation process.			

Theme 1 Increased Efficiency in the Registration Process

The concept of EAC-MRH is powerful as it will not only reduce time and cost to market for new products, as well as increase the market size for potential market entrants, but importantly will also ensure that citizens across the EAC receive similar access to life saving products. For the initiative to be truly successful though, it requires a harmonised process in law and a credible regulatory process in practice.

Pharmaceutical partners have suggested that thus far the timelines and registration process presented in the EAC harmonised regulatory process have not been credible. Notably, full parallel submission has not yet been implemented. The World Health Organisation's (WHO) Joint Assessment program has provided a temporary solution, assisting those countries who have more limited regulatory capacity such as Rwanda and Burundi. While this support is invaluable in building EAC capacity, leveraging WHO expertise too heavily means that EAC regulatory activities are aligned with WHO priorities rather than their own.

Pharmaceutical manufacturers are reticent to go through the EAC joint assessment or joint evaluation procedure as they do not yet have confidence in the process, and the benefits of harmonisation, while understood at a conceptual level, are not apparent at a practical level. Many pharmaceutical partners noted that they were taking a "wait and see" approach to the EAC-MRH project, continuing with normal in-country registration processes. In particular, they expressed a reticence to put any critical products through an uncertain route. Even those that have participated in the EAC joint evaluation process, noted that once that same dossier has been submitted through EAC, they are then required to send it to each country individually, and review there takes a further 3-4 months.

Development of stringent, common technical standards, documents and procedures, and an introduction of full parallel submission and manufacturing site inspections should serve as a basis for national registration decisions and will be an ongoing process at the EAC level. The long term vision and transition recommendations below outline implications on the volume and speed of review of new drug applications and the role of imports. Additionally, we outline ways for agencies within the EAC to both complement each other, pooling the workload, and to leverage the expertise and activities of Stringent Regulatory Authorities (SRAs).

LONG TERM VISION: Mutual Recognition

Mutual recognition is the ultimate goal of any harmonisation project. It is the process by which agencies have sufficient faith in each other's capacity and process that they are willing to automatically accept the findings of the review process. Four years into the EAC-MRH project, with donor funding designated for capacity building and strengthening of the NMRAs, the three members of the EAC with independent agencies (Kenya, Uganda and Tanzania) are moving towards mutual recognition between themselves. Like the Seychelles in the Southern African Development Community (SADC), who unilaterally recognise the results of the Zimbabwe regulatory review process, Rwanda and Burundi may choose to leverage the expertise of their EAC partners and recognise their results, building capacity over time to move to full mutual recognition within the five EAC member states (and indeed, any members who may join in the future). This long term goal is supportive of individual agency financial sustainability and supportive of wider availability of life saving medicines for EAC citizens as a whole, as through mutual recognition, NMRAs can individually achieve faster time for review, stronger, more consistent capacity, greater transparency and streamlined application processes, earlier approval of more drugs and vaccines and higher profitability through increased retention and import fees.

Feature 1.1: Harmonised Registration Process, Higher Fees

One consistent message back from pharmaceutical partners is that the total costs of registration dwarf the actual monetary fee charged. The challenge of having to file a slightly different dossier in multiple countries, and navigating different agencies with slightly different guidelines and capacities is a sizable drain on pharmaceutical resources and results in fewer products being taken through *any* EAC country's regulatory process.

It is worth noting that the fees charged in the EAC are relatively small compared to other regulatory bodies globally (see table below). Of note, the US FDA charges approximately US$ 2.4 million for a new drug application. Within the EAC, the fees charged by the member states for registration and maintenance are minor in the context of the overall cost of drug registration. However, for higher fees to be acceptable to pharmaceutical

applicants, and not detrimental to the volume of applications overall, they need to be accompanied by an increased credibility in the agency as a whole, and greater transparency in the review process. Indeed, of the multiple companies LHGP spoke with, not a single partner has expressed an unwillingness to pay larger fees for EAC registration *if the review time, dossier and process can be standardised*.

Table 1: Fee Structures Internationally, Comparative Regulatory Agencies

Current Process	*EAC average*	*India*	*South Africa*	*US*	*EMA*	*Austra-lia*	*Singa-pore*	*China*
Currency	US$	US$	US$	US$	€	AU$	US$	US$
Registration Fee	1,400	1,000	10,000	2,374,200	278,800	45,000	10,000	100,000
Annual Retention Fee	400	150	500	585,200	100,000	1,590	300	6,577
GMP Inspection Fee	5,800	5,000	20,000	190,389	179,000	120,000	24,000	20,000
Audit Frequency (years)	4	5	5	2	3	5	3	5
Processing Time (months)	14	9	6	10	7	6	6	N/A
% of Registration with WHO/FDA	35%	80%	80%	100%	100%	100%	100%	N/A
GDP (billion US$)	147	2,289	266	17,947	16,200	1,340	293	10,866

There is an inherent inconsistency between inflation, rising incomes and the cost of healthcare and static registration fees that are set in parliamentary legislation. The Chinese FDA, for instance, has recently increased their registration fees twenty-fold to around US$ 100,000, stating that the previous fees which were set in 1995 had become "severely inadequate". That said, it is important to consider fees in the context of economic attractiveness of the region and local manufacturing. China has a large national manufacturing base, and therefore may have other incentives behind setting high fees. The GDP of China is around US$ 11 trillion, around 70 times that of the EAC, and therefore represents a far more attractive commercial opportunity for any potential manufacturer. In contrast India has similar fee levels to the EAC (US$ 1,000), but a GDP of US$ 2.3 trillion. Similarly, China and India have very strong domestic manufacturing, and may wish to protect their national industries against imports through fees. While the EAC is similarly supportive of local manufacturing, with over 80% of products imported, it is not viable for either NMRA financial sustainability nor the health of EAC citizens to dis-incentivise importing at the current time. This report focuses largely on international pharmaceutical manufacturers, as the predominant drivers of NMRA revenues and providers of healthcare products within the EAC.

Table 2: Fee Structures in Countries with Similar GDP

	EAC average	*New Zealand*	*Peru*	*Chile*	*Vietnam*
Currency	US$	US$	US$	US$	US$
Registration Fee (US$)	1,400	1,075	125	2,231	300
Annual Retention Fee (US$)	400	659	50	250	150
GMP Inspection Fee (US$)	5,800	10,000	4,000	4,000	4,000
GDP (billion US$)	147	174	192	240	194

Currently, for each distinct product application done by a pharmaceutical manufacturer, the national agency charges a fee. These fees differ from one country to another. Currently the fees have been broken down into:

1. Assessment and registration fees
2. Annual retention fees
3. GMP inspection fees

Ultimately, within the harmonised EAC, the aim is true mutual recognition, whereby one agency conducts a review (potentially with the EAC acting as a coordinating body to allocate reviews among EAC member countries), and then the other member states in the EAC agree to recognise the result. This means therefore that within the three categories of fee:

1. The assessment and registration fee is paid to the implementing agency, to cover the costs of review;

2. Other EAC member countries receive retention and import fees once the product is approved;
3. Similarly, the implementing agency for GMP receives the inspection fee.

Within this structure, there would be room for fees to increase. Our modelling suggests that fees could be as high as $6,000 for the EAC *as a whole.* However, whilst much focus is placed on registration fees as a main driver of *revenues*, they are in fact a far smaller driver of *profit*, as NMRAs incur cost in the registration process. In contrast, retention fees and import duties provide a source of revenue to agencies that have relatively small associated cost. This is discussed further in Theme 2, but it is important to note that within the aim of financial sustainability and seeking out sources of revenue that allow for NMRA expansion and ongoing harmonisation activities, it is in NMRA interest to move towards mutual recognition of results, regardless of whether other agencies do too. With mutual recognition, even whilst agencies are not incurring the costs of review work, they continue to derive benefit from the harmonisation process. This also means that agencies can reduce their workload while still remaining as profitable as in previous years, if not more. There is precedent for this in other harmonisation initiatives, as seen in the table below.

Key Point:
While registration fees are an important driver of ***revenues,*** *they are a far smaller driver of* ***profit.***

Insights from Financial Modelling: In the case of Kenya, our modelling suggests that with only 60% of the current number of new drug applications processed, including 30% of which with an expedited review due to SRA approval, the Kenyan Pharmacy and Poisons Board's revenues would be flat, though profits slightly higher due to a reduced cost base.

Table 3: Examples of Mutual Recognition Internationally

European Union - EMA	EMA has signed Mutual Recognition Agreements (MRAs) with the following countries: ▪ **Australia:** Covering exchange of certificates of GMP compliance for manufacturers and batch certificates. ▪ **Canada:** Covering both human and veterinary medicinal products (excluding immunological products) and is based on the exchange of certificates of GMP compliance for manufacturers and batch certificates. ▪ **Japan:** Limited MRA applying to human medicinal products only and GMP for chemical pharmaceuticals, homeopathic medicinal products, and vitamins, minerals and herbal medicines considered medicinal products by both parties. ▪ **New Zealand:** Covering GMP inspection and batch certification for human medicinal products. A two-way alert system based on the European model is in operation. ▪ **Switzerland:** The fully operational agreement regarding mutual recognition of conformity assessment was initiated covers human medicinal products, GMP inspection and batch certification.
Canada	Canada has MRAs with the following countries and organisations: ▪ **European Community** for both human and veterinary medicines based on the exchange of certificates of GMP compliance for manufacturers and batch certificates ▪ **Switzerland**: Fully operational agreement ▪ **European Free Trade Association** (EEA EFTA): Fully operational agreement ▪ **Australia:** Covering human medicines only on conformity assessment regarding medicines and GMP inspection and certification ▪ Trilateral cooperation with the **US** and **Mexico** covers regulatory issues pertaining to drugs, biologics, medical devices, food safety and nutrition
US - FDA	The FDA has MRAs with various international organisations such as: ▪ World Health Organisation (WHO) ▪ International Conference on Harmonisation (ICH) ▪ International Cooperation on Harmonisation for Veterinary Products (VICH) ▪ International Cooperation on Cosmetic Regulation (ICCR) ▪ Global Harmonisation Task Force (GHTF).
Australia	Australia has signed MRAs with the following countries and organisations:

- **Canada** on conformity assessment regarding medicines and GMP inspection and certification
- **European Community** on standards and conformity assessment covering medicinal products, GMP inspection and batch certification and medical devices
- **Switzerland** and **Singapore:** Covering GMP issues

Higher fees in the future, once true mutual recognition is established, represent an opportunity for agencies to recoup some of the benefit from increased efficiency and workload pooling from manufacturers. Fee increases will be welcomed if they occur alongside increased speed to market. However, the volume of applications is not static, and if fees become too high relative to how onerous or slow the regulatory process is, pharmaceutical partners will simply bring fewer products through the EAC regulatory process. As the user fees charged in EAC countries are typically indicated by parliament, these will need to changed, ideally in a coordinated manner alongside the implementation of common acceptance of registrations.

Feature 1.2: Faster, Rigorous Review

Pharmaceutical companies repeatedly emphasised that "biggest enemy of the registration process is time". Some countries within the EAC, such as Tanzania, have offered expedited review processes but historically this has not seen timelines for review change substantially. The harmonisation process will likely lead to a surge in applications for new products, but with a division of labour, NMRAs will not only be able to process them, thus seeing revenues increase, but also reduce their historic backlogs.

The higher volume of applications will compensate for the pooled review process, and therefore the sharing of user fee opportunities for each individual country. It is only mutual recognition that allows NMRAs to increase their combined throughout without compromising on rigor of review – and therefore ensure that higher fees remain acceptable to the pharmaceutical industry.

Key Point:
Fee increases will be welcomed if they occur alongside increased speed to market, and lead to higher volumes of applications.

Feature 1.3: Mutual Faith in Capacity Across All Agencies and Information Sharing

One key feature of mutual recognition within the regulatory process is mutual faith in capacity across agencies and clear information sharing. In other words, the various stakeholders in the regulatory process need to have confidence in the capacity of the various implementing agencies, namely:

- NMRAs must trust in each other's ability to review applications with sufficient rigor to mutually accept recommendations;
- Pharmaceutical companies must trust that the review process and use of proceeds is sufficient to merit higher fees; and
- Patients and hospital administrators must trust that the quality of medicines passing through the review process are being maintained.

While EAC NMRAs may not yet be ready for true mutual recognition, the expertise sharing is already apparent within the EAC, for example through the mentoring relationship between the Ugandan NDA and the nascent Rwandan regulatory agency. The need for capacity building is immediately evident in Rwanda and Burundi, but similarly other agencies cannot rest on their laurels – the rapid nature of healthcare transformation and new medical products mean that regulatory agencies need to be constantly educating themselves to keep abreast of new developments. Of course, building capacity requires funding, but even unilateral recognition of results can contribute to this.

Insights from Financial Modelling: If Rwanda and Burundi were to accept the results of all Joint Evaluation processes over the next year, and introduce retention and import fees, they could theoretically be getting up to US$ 2 million and US$ 0.5 million in revenue respectively in 2017 prior to completing any new drug application reviews themselves.

As mentioned above, the first stage of the EAC project has developed mutually acceptable standards, leveraging guidelines borrowed from international bodies like the WHO, SwissMedic and ICH. Following a series

of joint assessment and joint evaluation sessions conducted alongside regulatory partners, EAC NMRAs have now established a benchmark for cooperation. To move to true mutual recognition, NMRAs now need to build familiarity which will form the foundation for trust and ultimately an automatic acceptance of each other's process. This requires a mutual faith in capacity between the EAC NMRAs. This mutual faith becomes even more important in the future, were NMRAs to specialise in particular areas, akin to the example of EMA. Once NMRAs in the EAC move beyond a joint evaluation process, and particularly in areas where one NMRA has more expertise than another, mutual faith in quality of evaluation and capacity will be critical for maintaining mutual recognition.

IMPLICATION: Faith, speed and reciprocity

Implication 1.1: Total Financial Self-Reliance

The aim of this project is to evaluate how EAC member NMRAs can become fully self-reliant, namely not dependant on receiving money from government, donors, or any other external sources. While the EAC project has to date been funded wholly by donors, in the long run NMRAs must look to be financially self-sustainable. Unlike many other regulatory agencies internationally, EAC NMRAs do not receive substantial budgetary support from their respective public bodies. Many benefit from in-kind support, such as personnel from the Ministry of Health, but in this project we have sought to establish a means for EAC NMRAs to be entirely self-funded.

This also raises a question of how financing flows are managed, both internally and between agencies and the EAC Secretariat. The simplest and politically viable approach is that fees will not be collected by one single body, but rather will be paid directly to the relevant agency. This reduces strain on human resources for financial management for any one agency or the need to transfer funding between different regulatory bodies. It reduces, but does not negate, the ongoing importance around appropriate transparency of use of funds. Particularly in the event that a stringent-regulatory authority waiver or expedited review is introduced, it will be of paramount importance to other regulatory agencies that in leveraging their expertise for an increased fee, those revenues are used wisely and to further support the harmonisation process.

In the event of full self-reliance, agencies are wholly responsible for the funds that they receive, and critically, have full ownership over use of proceeds. Self-reliance means that even within a harmonised regulatory system, NMRAs retain sovereignty over their cash flows, and therefore have the ability to determine how best to allocate their resources. It is our view that mutual recognition, and even unilateral recognition, supports this.

Implication 1.2: Harmonisation Leads to Increased Volume of Applications Overall

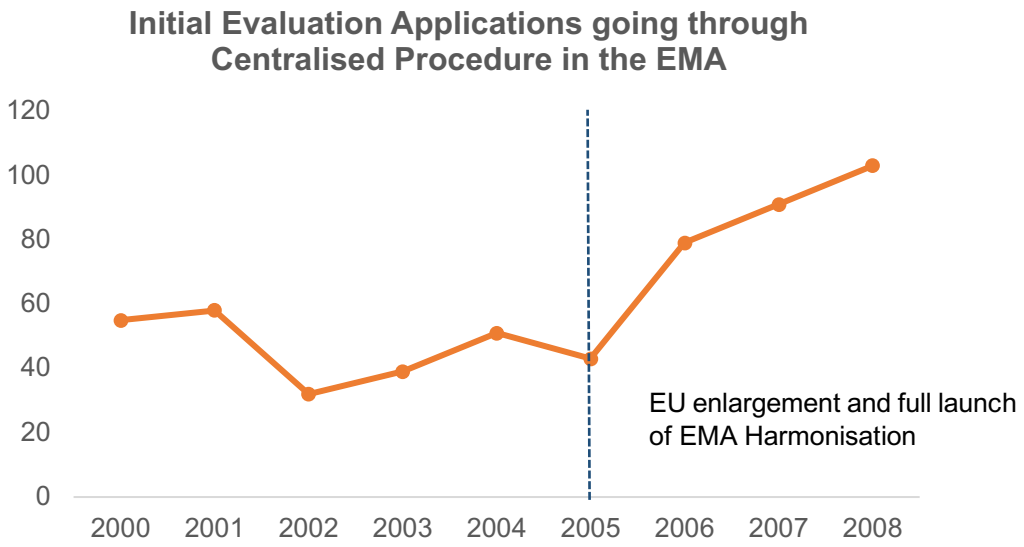
There are critically two dimensions that affect the revenue of the regulatory agencies – the fee charged for new drug applications, and the volume of drug applications. With the streamlining of the regulatory process of EAC-MRH, supply of drug applications will increase. Furthermore, this comes at a time when the healthcare sector in Sub-Saharan Africa is growing rapidly. Following strong growth in 2015, pharmaceutical manufacturing in Africa in general, and the EAC in particular, will continue to expand this year and going forward. This occurs in a context of a greater recognition of Africa's potential as a market for pharmaceutical products, nascent economic growth, a burgeoning middle class and private healthcare services industry. Although local drug manufacturing is growing, with increasing regional and foreign investment, the EAC largely relies on pharmaceutical imports to meet the bulk of its healthcare needs, and this is likely to continue. The broader economic context of each country, and the EAC as a whole, has implications for the healthcare market, and therefore, the incentives of pharmaceutical companies to bring products to the EAC market. Although the EAC is still a relatively small market by international standards, it is growing fast. In contrast, the South African pharmaceutical market alone is much larger than the entire EAC (US$ 3.7 billion), but its growth is expected to stagnate over the coming years.

> *"In the event of true mutual recognition, "the volume [of new drug registrations] will be **huge**".*
>
> *~ Pharmaceutical Manufacturer*

Insights from Financial Modelling: Even with mutual recognition and only the implementing agency receiving registration fees, the uptick in the number of different drug applications to the EAC as a whole would only have to be 5% per annum for the NMRAs to increase their revenue by 1.5 times by 2025 (with conservative assumptions of only 2% growth in revenues from imports and no government or donor funding).

The EAC is therefore well placed as a target market for international pharmaceutical companies. The EAC-MRH project means that hurdles towards bringing products to the EAC are reduced. Feedback from pharmaceutical partners suggests that in the event of true mutual recognition, and therefore a faith on the part of applicants to go through the process, there will be a considerable uptick in the supply of new drug applications for the EAC region. This means not only increased revenues from new drug applications, but also a larger body of medicines available in the EAC, larger imports, and therefore higher import fees. With these increased volumes, agencies can be as profitable even with a lower workload.

Figure 1: From 2005-2008 the number of initial applications for human medicines in the European Medicines Agency has doubled



Source: EMA annual reports, June 2010

Implication 1.3: Faster Registration Times & Reduced Backlog

The most important factor for new drug or vaccine registration on the part of the applicants is time. The importance of review times is relevant for pharmaceutical companies because an extended review process affects the commercial attractiveness of new medicines, as sponsors have to wait to begin to recoup the costs of research and development. In the US, the FDA estimate that a delay of one month in a review's completion costs its sponsor around $10 million. Faster review times, without compromising quality, confer advantages of:

- Reduced lead-time associated with meeting different country requirements;
- Significant cost savings to the pharmaceutical industry through reduced time-to-market; and
- Patients' quicker access to new and improved therapies at more affordable prices.

Key Point:
The most important factor for manufacturers regarding product registrations is ***time.***

While some joint assessment activities have been conducted previously, feedback from those groups that have gone through the joint assessment, and as such taken the risk of the uncertainty around the review process, is that they have experienced longer lead times than expected. From a perspective of financial sustainability and efficiency, review times are as relevant for the agency as for the pharmaceutical company. There is a direct

trade-off between review times and revenues, in terms of the number of applications agencies are able to focus on and therefore registration fee income, and in terms of recouping import revenues sooner.

As outlined in Theme 2, the main drivers of NMRA profit are maintenance fees and import charges, and as such the speed with which applications are reviewed has a direct effect on their revenue-generating potential. Faster review times means a larger number of applications can be reviewed, and likely a larger number received as pharmaceutical companies are incentivised to bring more products through the regulatory process, as well as shorter time until import revenues begin.

Insights from Financial Modelling: Our modelling suggests that even when assuming 12-month standard review process and 9-month SRA-expedited review process, by pooling resources and exploiting efficiencies of the harmonisation process (including the mutual review recognition), EAC as a whole will be able to process around over 3 times more new product applications per annum (assuming 30% of those applications would have a SRA-Waiver) than currently. This would allow Kenya to reduce their 1,500-item backlog within less than 2 years and with similar expenditure levels, increase overall profit by over 40%.

At present, review processes are duplicated across multiple agencies, therefore removing this through harmonisation will free up scarce agency resources. While concerns have previously been raised that a harmonised EAC may mean fewer new drug applications to each individual agency (and hence lower revenue from registration fees), the clear message back from potential applicants confirms that an effective and efficient harmonised structure would be adequate to incentivise increased applications, contributing to a far greater variety of products in each individual country

While the focus of this project is on the NMRAs, we would simply note that there are two sides to an application process, and timeliness equally rests on pharmaceutical applicants. Challenges of language, incomplete submissions or delays in responding to questions in dossier all contribute to a longer review process that is not the responsibility of NMRAs.

TRANSITION RECOMMENDATIONS: Ongoing Capacity and Trust Building through Joint Activities

Existing medicines regulatory activities in the East African Community are divided into three main areas:

1. National Review
2. Joint Assessment
3. Joint Evaluation

As outlined above, the long term vision for harmonisation should be mutual recognition of NMRA member agencies. There is a reticence among NMRAs to eliminate national registration entirely, and indeed, we have sought to preserve national sovereignty within the NMRAs through other mechanisms outlined further in this report. While NMRAs may move to be harmonised, they operate within different country contexts. Incentives for pharmaceutical partners to register and import their products to a particular country or region are a product of both the regulatory system and the economic environment. Kenya, as a member of the EAC with approximately half the total GDP of the whole East African Community has a particular responsibility to ensure continued coordination with other NMRAs as it is relatively more attractive as a target market and therefore viable as an independent NMRA. If the benefits of harmonisation are not apparent to pharmaceutical partners, there is a risk that they may continue to target Kenya as a first point of call whilst the review and approvals process remains unclear at the harmonised level.

While commendable and valuable, this regional harmonisation process could have two implications for both the burden and the support on regulatory agencies:

1. New and potentially higher standards in processing applications; and
2. Reduced opportunities to collect fees, unless off-set with additional applications.

While the application of higher standards is important and the process for harmonised, rigorous standards in reviewing new drug applications is now well established, our modelling suggests that concerns about reduced *registration* fee revenue and their impact on NMRA financial sustainability are unfounded.

Recommendation 1.1: Fees Remain at Current Levels

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NMRA fees are typically set by national parliaments of the EAC member countries. This means that changing them is difficult and requires a lengthy process. As noted above, China recently changed their registration fees after more than a decade. Therefore, in the immediate future, we recommend that each agency continue to charge their designated registration fees. The total of US$4,250 is the current total fee for registration across EAC member countries. Our modelling suggests that a total fee of up to US$ 6,000 is viable for registration in a truly harmonised EAC. This allows some room for incremental fees to Rwanda and Burundi should they establish independent regulatory agencies with the capacity to charge fees.

Table 3: Fees and Throughput for Each Agency

Current Process	*Kenya*	*Uganda*	*Tanzania*	*TOTAL*
Registration Fee (US$)	1,000	1,250	2,000	**4,250**
No of registrations per year	500	400	450	**1,350**
No of outstanding registrations	1,500	673	650	**2,823**
Personnel	180	146	300	**626**

Over time, agencies may seek to harmonise fees, though this is not necessary. In the EAC Tourist Visa initiative, individual entry visas remain at different price points despite the establishment of a common border visa. Once the harmonisation project is well established, agencies may move to harmonise and potentially to increase fees, but this is part of the longer term view and should only occur once mutual recognition is in or near in place.

Key Point:
Fee increases are feasible but only once a truly harmonised process is in place.

Case Study: The East African Community Tourist Visa

There is precedent for mutual recognition of regulatory activities within the EAC in the EAC Tourist Visa. Kenya, Rwanda, and Uganda created Borderless Borders to open new opportunities for travel throughout the region. The Single Tourist Visa came into effect on 1st Jan 2014. Under the agreement reached by the three countries, Rwanda provides the software for personalisation of the visa stickers to Kenya and Uganda. The software enables the other countries to share the fees, tourist information and tourism data.

The fee of $100 is paid in full at the point of entry to the EAC, with $40 payable to the administering country. The other two partners will receive $30. While it is hoped Burundi will join the regime at a later date, Tanzania opted to stay outside the common tourist visa initiative. While the monitoring software maintained by Rwanda in theory allows for redistribution of revenues, it is likely that the reasoning for this opt-out was at least in part a concern from Tanzania that the mechanism for revenue sharing was not reliable, and under the new system Tanzania would miss out on potential visa revenues.

Unlike the East Africa Tourist Visa however, our recommendation is that in a harmonised EAC drug registration and retention fee payments would all be paid directly to the relevant agency, so that no group has responsibility for reallocation of funds.

Recommendation 1.2: Scaled Down Joint Evaluation Sessions

R P F C

Currently, the number of staff attendance at joint evaluations ranges from between 20-30 from each NMRA. After two years of Joint Evaluation sessions NMRAs have expressed a reticence to move to full mutual recognition, but have themselves suggested a shift to more scaled down participation in the Joint Evaluation sessions. This is based both on the need to ensure financial sustainability of the Joint Evaluation sessions and

on a foundation of trust and common processes that has been established through earlier sessions. With a delegate from each of the three main agencies of around 10 people, net costs to the NMRA including travel and accommodation will be approximately neutral. Each agency would be paid their full registration fee and this is sufficient to cover their costs. While the host country would have incremental costs of hosting, other countries would support travel and accommodation for their staff.

Table 4: Joint Evaluations for New Drugs

	Current Process	Scaled Down Process
No Personnel per session	75	30
No sessions per year	4	10
No products being evaluated per session	8	10
Total no products being evaluated per year	32	100
Joint evaluation cost per year (US$)	**160,000**	**300,000**
Cost per product being evaluated (US$)	5,000	3,000
Total fees paid per product (US$)	4,250	4,250
Registration fee revenue per year (US$)	**136,000**	**425,000**
Net profit / cost per three agencies (US$)	**(24,000)**	**125,000**

The total cost for a Joint Evaluation session is estimated at US$ 40,000. With an average of 8 products, and the current NMRA fee structure, the revenues available for the evaluation of those products is US$ 136,000. These sessions currently occur once per quarter. As demonstrated, the sessions can be self-financing, and even profitable, and as such could be scaled up gradually to once a month. Profits from Joint Evaluation sessions could be used to support the attendance of Rwanda and Burundi at these sessions, along with explicit learning sessions. With approximately 10 products for each session, this means the throughput each year for products undergoing Joint Evaluation could be around 100.

These joint evaluation sessions, where all five EAC NMRAs work together, are crucial for building mutual faith in capacity and trust. These sessions are how EAC NMRAs can create the confidence to move to mutual recognition. We would recommend a structure whereby each country receives their existing registration fees, but that the outcome of the review process is a common judgement without additional processes in national jurisdictions to allow access to market. At the moment, once registered at the EAC following joint evaluation, the application still requires national submission for processing. The logical next step of this ongoing process is mutual recognition, whereby once mutual faith in capacity is established, then acceptance of each other's results can be automatic.

In our conversations with different agencies, some have indicated that a discussion of mutual recognition is premature, while others are happy to move ahead on the basis of previous joint evaluation work. It is our view that even unilateral, rather than bilateral or mutual recognition will be supportive of financial sustainability in the individual NMRAs. Either way, joint evaluations are critical to sustain the goodwill that has been built up over the previous years of joint evaluation, and can continue by leveraging the existing funding arrangement.

Recommendation 1.3: Scale up Joint Assessment Activity with Opinion Issued 

Joint Assessment activities are an alternative to Joint Evaluation sessions, whereby two or more NMRAs within the EAC conduct a review simultaneously, potentially supported by an external regulator such as the WHO. Akin to the joint evaluation process, this may be self-financed by countries with established NMRAs. This does not apply to those countries who require ongoing learning and mentorship, and do not have internal NMRA funds, or of other countries such as Ethiopia acting as observer to the review process. The reviewing NMRAs, for example Uganda and Tanzania, could then issue a joint opinion, and share the review dossier. Other member countries would then have the option to move that opinion into a national recommendation or approval. The implementing agencies would be paid their established registration fees. Akin to the process in ZAZIBONA, products that meet assessment criteria are then granted registration in the participating countries, but this does

Insights from Financial Modelling: According to our modelling, this is perfectly manageable within the EAC assuming agencies exploit efficiencies of the harmonisation process like the joint evaluations for new drugs or SRA-expedited review process.

not replace the need to register in each country in line with national requirements, but rather to collaborate and hence mutually leverage agency resources. The assessments looked at common application among the four NMRAs. If a product had submitted an application in at least two jurisdictions it could be considered as a candidate for joint review.

As in ZAZIBONA, joint assessment activities which have historically been supported by the WHO, but are moving to NMRA support. Each NMRA set aside a portion of the application fees for the products that are jointly reviewed towards the cost of the joint assessment session. This ensured sustainability of the project with or without external support. This is a second mechanism through which to build faith in mutual capacity. Over time, as EAC member countries find a dearth of disputes with the opinions issued by other joint assessments, they may feel more comfortable in moving towards mutual recognition.

Case Study: ZAZIBONA, Joint Assessment and Sustainability

ZAZIBONA is a collaboration between four national medicines regulatory authorities (NMRAs), namely Zambia, Zimbabwe Botswana, and Namibia. The four NMRAs were to work together as an experiment as a way to improving efficiency in medicine registration in the region. Due to the success of this initiative, other southern African countries have shown interest to join the arrangement.

The case of ZAZIBONA is similar to the EAC harmonisation initiative as it is aimed at:

- Provision of good-quality medicines in the region;
- Significant reduction in time taken to grant marketing authorization (registration) in the individual countries; and
- Efficient utilisation of resources within regional national regulatory authorities through work sharing.

According to the arrangement, a company that has submitted an application in two or more of the member nations would be approached with a proposition to be assessed jointly. The lead nation, Zimbabwe, would determine where the join assessment will be carried out generally on a rotational basis. The host nation would cater for the accommodation and venue expenses while other member states would send qualified assessors to the joint assessment and incur only the transport and per-diems of their respective officers. The results from this assessment is adopted by all the member state who would finalise the registration in the individual authorities.

The pharmaceutical company pays a registration fee to all the NMRAs, however, Each NMRA set aside a portion of the application fees for the products that are jointly reviewed towards the cost of the joint assessment session. This ensured sustainability of the project with or without external support.

The ZAZIBONA collaboration does not represent the replacement of the need to submit applications for registration in a single participating countries in line with national requirements. However, in order to facilitate cooperation among ZAZIBONA authorities, certain modifications were made to the individual application processes.

Recommendation 1.4: Streamlined GMP Approvals Process

The EAC chose to adopt the Good Manufacturing Practice (GMP) guidelines from the WHO and customised them to suit the EAC region. However, not all the countries in EAC have that capacity to perform GMP audits (namely, Rwanda and Burundi, who lack the staff and technical capability to carry this out). Currently, aside from Joint GMP Assessments, Kenya, Uganda and Tanzania are conducting their own GMP inspections, a sizable cost for both NMRAs and manufacturers. Further streamlining GMP approval process represents a win-win for both pharmaceutical partners and NMRAs.

Interviews with pharmaceutical partners repeatedly emphasised that one of the largest costs in the new drug registration process is GMP site visits. GMP inspections are associated with manufacturing disruption and considerable human resource costs on the part of the manufacturer being visited. Many of these sites,

particularly those located in Europe or Northern America, have already been successfully audited by one or more Stringent Regulatory Authorities (SRAs). As such, visits from EAC NMRAs may in some instances provide limited incremental assurance on quality. The streamlining of GMP inspections represents a low hanging fruit in the harmonisation process, and a means to garner significant goodwill from pharmaceutical partners.

Key Point:
Streamlining GMP site inspections is a low-hanging fruit and will engender goodwill from pharmaceutical manufacturers.

GMP site visits are also a large cost sink for NMRAs, and currently with each NMRA conducting this individually, it represents a sizable combined cost. We would recommend one inspection, either by a single agency or in the short term, joint inspections, with mutual recognition of the findings. Applicants may be stratified by perceived risk, with low-risk manufacturers subsequently receiving only desk based review. This could leverage the expertise of SRAs. There is precedent for this within the EAC. Uganda's NDA has already enacted a procedure whereby after the first visit, they simply conduct a desktop review for sites that are already inspected by an SRA without requiring repeated on site visits. Manufacturers are required to submit a file certifying compliance, but the re-inspection process is considerably reduced for SRA-approved sites. While we do not recommend that regulatory agencies within the EAC relinquish the ability to do site inspections entirely, and indeed, do not view this as politically viable, if Kenya and Tanzania were to follow Uganda's precedent in reducing the re-inspection burden and duplication of multiple GMP site visits, then efficiency in the overall drug registration review process would be improved considerably. Rwanda's existing activities leverage SRA site inspections, and expects to continue this protocol once their independent agency is launched.

Case Study: ASEAN

On November 29, 2004, the ASEAN Secretariat issued a media release entitled ASEAN Accelerates Integration of Priority Sectors following 10th ASEAN Summit. Eleven priority sectors, including health care, of which pharmaceutical products are a component, were identified. An ASEAN Sectoral Mutual Recognition Arrangement (MRA) on GMP inspection for manufacturers of medicinal products, was one of the priority initiatives. Taskforce on GMP Inspection was formed in 2005. Singapore and Malaysia were appointed as the Chair and co-Chair of taskforce.

As of August 2015, four ASEAN member states - Indonesia, Malaysia, Singapore and Thailand - had signed the agreement. The scope of the agreement covered medicinal products in finished dosage forms, including over-the-counter and prescription medicines. Following this, ASEAN Member States are obliged to accept GMP certificates or inspection reports from the Taskforce.

This reduction in GMP site visits for those sites already approved by an SRA is part of a wider theme of NMRAs in the EAC avoiding duplication in their activities, and improving the efficiency of their operations by building out capacity instead on new products targeting the EAC specifically and Africa more broadly. This extends also to quality control and pharmacovigilance. We note however that NMRAs have raised concerns about some manufacturers, particularly those located outside Europe or Northern America, where while a site may be SRA approved but the production lines for products differ depending on the target market. It is for this reason that we suggest stratifying GMP approvals by perceived risk of the manufacturer.

Insights from Financial Modelling: By examining historical financials and modelling out projected costs, our modelling suggests that reducing duplicated GMP inspections by 50% would cut the non-wage related cost base for the Tanzania Food and Drug Authority by 18.7%. This means that while fees would decrease slightly, costs would decrease further – taking the example of Tanzania, revenue from GMP inspections would decrease (though revenues would still increase overall) by 3.9% but the reduction in non-wage related costs is larger, meaning a relatively larger increase in profit.

Recommendation 1.5: Expedited Review for those Products Already Registered by Stringent Regulatory Authorities

Healthcare is truly a global industry, and while local manufacturing is expected to grow in the future, currently the EAC relies heavily on imported products. The vast majority of the pharmaceutical partners importing to the EAC, and undergoing regulatory approval with the EAC NMRAs are also supplying other international markets and as such, are regulated by other international bodies. The EAC can leverage the work done by other SRAs to avoid duplication and increase the efficiency of their review process. Recognising the enormous value of leveraging the expertise of other agencies and international stakeholders like the European Medicines Agency (EMA), the US Food and Drug Authority (FDA), and the World Health Organisation (WHO) is a valuable way for EAC regulators to learn best practice, however the importance of applying such lessons into the local context is paramount. In leveraging the resources of these agencies, the EAC must retain an ability to determine local suitability and relevance for the East African population. Many smaller countries already leverage the WHO's Prequalification Process (PQP) as a proxy for their own regulatory reviews, though this is most in situations where international donor agencies are planning on purchasing sizable volumes for in-country use.

Key Point:
Agencies can charge a higher fee for SRA-expedited review, provided it is associated with a faster review time.

The concept of a SRA expedited review is well known, and there are a number of international regulatory agencies that already implement this, such as Singapore. This mechanism has previously been discussed in the EAC context. It has the potential to reduce the strain on regulatory agency resources, increase the volume of drug applications into the EAC, and increase fee revenue. It is likely that most multinationals would want to use the fast track service even if it meant a substantially higher fee since the fee itself is a minor component in their overall cost calculations. The reduced uncertainty around whether an application that was already approved by another regulatory body would be accepted in the EAC would also increase the attractiveness of entering that market by lowering the cost, and increasing speed to market.

Insights from Financial Modelling: In our conversations with different agencies, we found out that between 30-70% of drugs currently registered in the EAC member countries have also been previously approved by an SRA (such as WHO prequalification). Our modelling suggests that if we conservatively assume that 30% of new product registrations fall into this category, introducing an SRA-expedited registration process for new products that allow for 9 months processing time as compared to 12 months for full application and desktop GMP dossier review, would be associated with approximately 16% (or US$ 2 million between 2017-2025) overall agency cost savings on registrations.

Feedback from pharmaceutical partners has reiterated that they would be happy to pay a higher fee for SRA-review, provided it is associated with a faster review time. For the NMRAs, the accelerated registration time results from a less labour intensive process, meaning lower agency costs incurred. For manufacturers, the ability to leverage clinical review already completed by SRAs means a less onerous registration process with greater clarity and transparency.

What is critical about this, is that by leveraging the expertise of international regulatory agencies, SRA-expedited reviews have the potential to attract higher fees (though for the time being, these should remain equivalent to those charged for national registration until agencies can be confident that they can commit to a faster review time) with lower NMRA costs. In this way, SRA-expedited reviews have enormous potential to contribute to NMRA profitability compared to standard reviews. Pharmaceutical companies are very supportive of this, as it has the potential to reduce processing time, their single largest concern, while this recommendation may also contribute to increased NMRA efficiency and profitability without compromising rigor.

It is important to emphasise that an SRA-expedited review would *not* seek to supplant the national authority of the NMRAs in their own geographies, and that relevance of products to local populations would still require assessment on the part of the EAC regulators. It is also important to distinguish between the viability of expedited review for well-established therapies, such as generics or over-the-counter medicines, compared to new therapies with more limited evidence and use bases, which will still require carefully considered review. The development of expertise for new products specifically targeting the EAC is

Key Point:
*SRA-expedited review means **higher fees** for **lower costs**.*

a further theme of these recommendations, Finally, in the context of the EAC and the *perception* among some international stakeholders that funds may be used inappropriately, it is important that such a recommendation is carefully managed to ward off the potential for exploitation and a perception that higher fees are associated with a more favourable review. As noted previously, transparency is critical here, and plays an important role in the willingness of pharmaceutical companies to pay higher fees.

Case Study: Leveraging SRAs in Ethiopia

Applications for products that are also registered with a regulatory authority of a member of the International Conference on Harmonisation (ICH) or a regulatory authority associated with an ICH member, are considered to be products registered with a Stringent Regulatory Authority.

Seeking to leverage this in the efficiency of their operations, the Food, Medicine and Health Care Administration and Control Authority of Ethiopia (FMHCACA) developed guidance for products registered by SRAs. The protocol eliminates dossier submission and means that the FMHCACA only conducts a full assessment of the product when deemed to be necessary. This procedure facilitates speedier registration of products previously-accepted through the WHO Prequalification Programme (PQ) and other SRAs in order to increase the availability of vetted medicines to Ethiopian citizens.

The rationale behind the introduction of these procedures is that:

1. Most of the requirements and principles stipulated by FMHCACA for approvals are derived from those developed by ICH countries or the WHO;
2. Full assessment of dossiers can be done at any time if deemed necessary; and,
3. The clinical studies and the benefit of the medicines for the general public health benefit have been accepted.

In Ethiopia, this process has reduced the time taken to register a product from 12-18 months to 6 months for qualifying products. In addition, the backlog of drugs pending registration has significantly reduced. The Common Technical Document underlying the EAC approvals process is based on ICH standards, and therefore the EAC is well placed to leverage the expertise of ICH regulatory partners globally in ensuring access of EAC citizens to life-saving medicines. As Ethiopia is currently an observer to the EAC, the decisions taken throughout the harmonisation process will have direct bearing on their ascension to the EAC in the future.

Similarly for GMP, Ethiopia conducts a desk based review of a dossier for those applicants with a valid GMP certificate from an SRA, which amounts to checking that all the requirements are complete and certified, only progressing to a full review if there is cause.

Recommendation 1.6: Increased Mentorship Program to Build Capacity

While there have been some moves to establish a twinning or mentorship program to build capacity for Rwanda and Burundi within the EAC, this is relatively unstructured and not well established. Rwanda has been partnered with Uganda, Burundi with Tanzania and Zanzibar with Kenya. An effective capacity building relationship requires clear accountability for both provider and the recipient, as well as a clear definition of what success looks like. Currently, this is not a structured or institutionalised relationship. This program could be developed through the use of observers and participants in Joint Evaluation and Joint Assessment sessions. While Burundi does not yet have an independent regulatory agency, Rwanda expects to launch one later this year. Rwanda and Burundi may still receive fees from imports and retention fees, and use this to fund their participation in the evaluation sessions.

Insights from Financial Modelling: If Rwanda and Burundi were to accept the results of all Joint Evaluation processes over the next year, and introduce retention and 2% import fees, they could theoretically be getting up to US$ 2.5 million in revenue in 2017 prior to completing any new drug application reviews themselves. These funds could be used to fund their participation in the joint harmonisation initiatives and for future capacity building.

Recommendation 1.7: Agencies move towards *Unilateral* Recognition in Select Areas

As noted previously, our modelling suggests that unilateral recognition of results by individual NMRAs is supportive of financial sustainability, regardless of the position of the other member NMRAs. Four years into the EAC harmonisation project, NMRAs are beginning to establish mutual trust and faith in capacity. However, there is no single one political force that can ensure that all EAC member NMRAs are willing to accept mutual recognition. NMRAs will and should act in their own self-interest. It is our position that each agency has a vested interest in moving towards mutual recognition from the perspective of financial sustainability. Registration fees should not be a barrier to this, because imports and retention fees are far more important as a contributor to profit. Uganda's National Drug Agency has recently taken the step of unilaterally accepting reviews done by SRAs, and their counterparts in the EAC, the Kenya Pharmacy and Poisons Board and the Tanzania Food and Drug Administration.

Key Point:
*Even **unilateral recognition** is supportive of ongoing financial sustainability.*

The smaller members of the EAC, Rwanda, Burundi and Zanzibar, can also move to unilateral recognition within the EAC. For example, in SADC, the Seychelles automatically accept the Zimbabwean national drug register as their national register. NMRAs and member countries are ultimately the drivers of harmonisation. Our modelling suggests that while EAC-wide mutual recognition may not be politically viable, unilateral recognition remains supportive of individual NMRA financial sustainability.

Insights from Financial Modelling: If Uganda were to unilaterally accept an additional 200 products from Kenya's roster per annum, the incremental revenue from retention fees would amount to US$ 4.5 million by 2025.

Conclusions: Increased Efficiency in the EAC NMRAs

Regulatory harmonisation can reduce the hurdles which a manufacturer needs to overcome to take their product to market, and in doing so increase the attractiveness of entering that market, but it cannot create a market where there is none. Pharmaceutical companies go through several phases in bringing a product to market, beginning with product development, followed by clinical evaluation. Following a successful Phase II trial, the costs to a company increase exponentially, as they must embark on a Phase III efficacy trial, alongside development of manufacturing capacity and regulatory approvals processes. The decision whether to progress at this key point is determined by the commercial attractiveness of the product. Similarly, once a product has already been approved in some markets, the decision whether to take that product into a new market is determined by the potential payoff of entering that market.

The focus of NMRAs is simply on the regulatory approvals process, but it benefits from being considered in the context of the drug development pathway and expenses. The African continent is viewed as a difficult market from the perspective of international pharmaceutical companies – not least due to its relatively small size (though they recognise the growth potential) and need to interact with multiple agencies. Perhaps the clearest contrast is India, where despite there being many states with different populations, budgets and healthcare priorities, one agency can give approval for the whole country. The regulatory process does not enhance this, with countries operating independently, requesting differed individual and national requirements for marketing authorisation. Appetite from pharmaceutical companies to enter the East African market is what will ultimately determine the supply of new drug applications, and therefore a key component (volume) of agency revenues from user fees. This is exactly the kind of problem that EAC-MRH seeks to address.

The recommendations outlined in the first section of this report have established a politically viable pathway to enhance the efficiency of NMRA operations, particularly as it relates to the review and registration process for new products. While much of the concern around financial sustainability of the NMRAs in the EAC-MRH process focuses on registration fees as a predominant source of revenue, our analysis shows that considering profitability as the main indicator of an agency's ability to support ongoing harmonisation activities and growth in internal capacity is a more useful means by which to assess appropriate changes to the registration process going forward. As noted above, an almost-exclusive focus on registration fees is unwarranted, and the revenues

and associated profitability from retention and import fees are relatively far more important. Through this lens, it is clear that moving towards mutual recognition with the transition recommendations outlined in this section is within each NMRA's own best interest, regardless of what other agencies choose to do.

Theme 2 Maintenance

While much of our earlier work around financial sustainability in the NMRAs focused on registration fees, further feedback and analysis of individual agency historical financial statements shows that ongoing sources of revenue like import duties and retention fees are relatively far more important for ongoing profitability. They constitute far larger contribution to agency profits and as such are a more sustainable and important source of funds for NMRA expansion and harmonisation activities. The example of Kenya below is particularly striking because Kenya's level of import duty is relatively lower than other NMRAs (0.75% compared to 2% in Uganda and Tanzania).

Table 5: Example of Kenya and the Relative Contribution to Revenue of Different Fee Sources

Kenya	Drug Registration	Maintenance	Imports
Fee	US$ 1,000	US$ 300	0.75%
Direct Cost to Agency	US$ 1,833,834	Minimal	Minimal
FY2015 Revenue	US$ 2,190,000	US$ 2,550,000	US$ 1,756,664

LONG TERM VISION: Growing Healthcare Market Drives Agency Sustainability

While every new drug application that is reviewed costs the NMRA almost as much as the total fee received, in contrast import duties and retention fees are driven by economic factors and an increase in revenue from either of those sources is not directly tied to an increase in agency activities. The EAC as a region is well positioned for economic growth, due to a transformation in the drivers of economic activity from agriculture to a wide range of other sectors, as well as an improvement in the regulatory environment for businesses as a whole. In healthcare, the EAC member countries are expected to grow considerably, with market estimates suggesting that both the pharmaceutical industry and the healthcare market as a whole will grow by at least 9%.

Table 6: Expected Growth Rates for 2016 in EAC Healthcare

Expected Growth Rate (local FX)	Pharmaceutical Industry	Healthcare Industry
Kenya	14.5%	10.5%
Uganda	9.3%	9.0%
Tanzania	13.6%	9.9%

Feature 2.1: NMRAs harness EAC Economic Growth for Financial Independence and Sustainability

A growing pharmaceutical market leads to growing imports and retention fees, which are the biggest drivers of profitability for NMRAs. Both our modelling and economic forecasts suggest that funds available from these sources will increase going forward, and can be used to support harmonisation and agency expansion. It highlights why a focus on registration fees as the predominant driver of agency revenues is too narrow, and equally suggests that NMRAs would be far better placed to focus on ongoing sources of revenue for financial sustainability. These figures also highlight how a unilateral move to recognition of results, both for registration of products and GMP site visits, are conducive rather than obstructive to NMRA financial sustainability considering their impact on revenues.

Table 7: Contribution of Registered Products to NMRA Revenues

	Import Fees as % of Revenues FY2015	Retention Fees as % of Revenues FY2015
Kenya	22%	32%
Uganda	51%	25%
Tanzania	37%	15%

What these figures show is that mutual, or even unilateral, recognition is beneficial for NMRAs because through import fees and retention fees following successful registration, they are generating profits from work done by other agencies in addition to their own product reviews. Furthermore, this highlights the importance of expediency in the review process, an added incentive to pool registration work in order to reduce backlog, as

Key Point:
With mutual recognition, NMRAs are generating profits through import fees and retention fees from work done by other agencies.

the earlier the agency registers a drug, the earlier they start receiving import duties and retention fees. As import duties on pharmaceutical products contribute up to half of all revenues to the NMRAs, this means that an exclusive focus on registration fees fails to capture the full picture for agency financial dynamics.

Feature 2.2: NMRAs collate Internal Data to provide Market Information about the EAC and thereby Enhance Attractiveness as a Target Market for Imports

However, import duties and associated agency revenues are tied to the growth of the healthcare industry in EAC countries and as such less able to be influenced by NMRA or EAC regulatory policy. As noted previously, the economic outlook for Africa is strong, with health care expenditure expected to grow by 11% by the year 2020 to keep up with the growing healthcare demands of an estimated population of 1.3 billion. This makes the continent a high-potential market for the pharmaceutical business. However, stringent regulation, lack of specialized skills in the pharmaceutical sciences and related disciplines, and strong downward price pressure, have historically made pharmaceutical manufacturing for/ in Africa challenging. The relative size of the revenue contribution of imports means that agencies have a financial incentive to decrease review times, as quicker review means quicker import revenues. This revenue is independent of the volume of new registration applications that are processed in future years, and linked rather to a stronger health system in EAC countries. Agencies can however improve the efficiency of the import duties revenue, and contribute to greater certainty about the commercial attractiveness of EAC markets through more effective data collection and expertise sharing mechanisms.

At present, Africa is heavily reliant on imported medicines. For example, 80% of the antiretrovirals keeping more than 5 million African people alive come from abroad[1]. While we believe the EAC-MRH will encourage local production of medicines, much of this innovation will occur in partnership with other developed and emerging economies. EAC can position itself to support and benefit from a growth in African production, both within the EAC and leveraging future supply from other African markets such as Ethiopia and Nigeria, both of which have ambitions to build strong domestic pharmaceutical sectors. In addition, due to complicated distribution lines, any global company looking to work in Africa would consider a partnership with local products/ packaging/ fill-finish hubs as attractive.

While to some extent the economic environment is outside NMRA control, agencies can contribute to an attractive market by both reducing the burden of the regulatory process, and by providing clarity on ongoing maintenance requirements for manufacturers. This ensures that the hurdles to imports and retention fee revenues are as minimal as possible from a regulatory perspective.

Key Point:
Anonymised NMRA import data is valuable market information that can be used to incentivise further imports and new product applications.

IMPLICATION: Increased Agency Independence from Registration Revenue and External Funding

A recognition of imports and retention fees as the predominant driver of NMRA profitability allows NMRAs to appreciate the independence that those revenue streams bring, both from other NMRAs, and from the drains on their own new-product review activities. These incremental funds can be used for an increased focus on market surveillance and import collection, as well as a scaling up of pharmacovigilance activities.

Table 8: Fee Structure for Revenues from Maintenance

Country	Import Fee Rate	Retention Fee Rate
Kenya	0.75%	US$ 300
Uganda	2.0%	US$ 500
Tanzania	2.0%	US$ 300

[1] Source: UNAIDS

There is even room to increase import revenues in some markets. Kenya for example has only recently introduced import fees, and these remain below the EAC average of 2%. By providing market clarity on compliance requirements, and allowing rapid access to economic markets when appropriate, individual EAC member countries can further enhance their attractiveness as a destination for imported pharmaceutical products, leading to a larger volume of drugs registered that are then paying imports and retention fees, which in turn are associated with greater NMRA financial independence and sustainability.

TRANSITION RECOMMENDATION: Regulatory Environment Supports Imports

Recommendation 2.1: Clarity in Guidance around Compliance

In early exploration of the EAC market, we examined some data around imports that suggested that even when products are registered, they may not actually be imported or sold. This finding was based on evidence from Zambia, arising out of a project between Medicines for Malaria Ventures and IMS. The IMS study found that for metronidazole in Zambia, while there were 47 products registered, only 10 were actually imported in the year of analysis. This means that pharmaceutical companies are paying a retention fee without actually accessing the market. Similarly, for hydrocortisone, of 31 registered products, only 8 were imported.

This raised questions in our analysis around why a pharmaceutical company would go to the trouble of registering a product but then not import it. Further exploration of the issue and conversations with stakeholders found two factors to be relevant. Firstly, there seems to be a general shift in the pharmaceutical industry from "splattergun" registration with little regard to ensuing costs, to a more strategic market targeting; and secondly, a rising concern around the cost of remaining in line with changing compliance requirements.

On the former, pharmaceutical partners emphasised that they were increasingly rationalising their resources, and instead of registering a particular product globally, are thinking more carefully about which geographies made sense in terms of commercial and public health. The second aspect is that remaining compliant with a product registration proved to be costly in the face of unclear guidance. Some groups indicated that this was in fact relatively more burdensome than initial registration. This sheds some light on the puzzling question of why some drugs may be registered and incurring annual fees but not imported – if the presentation of the product changes slightly, pharmaceutical partners may choose to cease imports because of a lack of clarity or excessive costs around remaining compliant and the process by which product and packaging changes are submitted and re-approved. Furthermore, pharmaceutical partners indicated that they may not even go through the initial registration process if they are unsure about the maintenance and compliance requirements. Additionally, if the compliance requirements are more onerous at the EAC level, this dis-incentivises companies from registering through the EAC harmonised process. Local manufacturers in the EAC have thus far been reluctant to engage because EAC countries have been waiving the need to conduct bio-equivalence tests, while the new EAC guidelines would require them.

> ***Key Point:***
> *Unclear guidance on compliance leads to reduced imports and therefore reduced agency revenues.*

This is particularly relevant if companies expect product presentation updates in the future. If the regulatory authority is not well organised to review the variation and provide feedback on whether the change is acceptable locally, or if this is not well communicated to international pharmaceutical partners, they will refrain from taking products through the registration process. Compliance is a key concern to multinational importers, and they will not supply a product locally if they are unsure they can ensure compliance. This lack of certainty means that EAC countries and citizens may have inferior products registered simply because updates are not being taken through the regulatory process. Beyond the importance to public health, this additionally means that NMRAs are losing out on revenue from imports on updated products due to a lack of clarity on compliance.

> **Insights from Financial Modelling:** We have not included this in our financial model, therefore our findings are conservative compared to the increased revenue generating potential for NMRAs through the creation of clear EAC maintenance protocols and process.

This is one key area for future harmonisation focus. There exists currently considerable variation in the specific regulation surrounding how different EAC countries carry out regulation activities. For example, the

management of similar infractions by manufacturers may be handled differently - where one NMRA might require that producer temporarily cease operation, another may give a warning and allow time for correction of the infraction. Part of the harmonisation process will require a considered series of discussions around the mutually acceptable standards that may allow for mutual recognition of regulatory approvals. Language may also be a challenge, as Tanzania and Zanzibar do most of their training in Swahili as opposed to English, while English remains the predominant language at the management level.

The importance of maintenance as a source of agency profitability reiterates the importance of NMRAs to ensure that they do not focus exclusively on new product applications for harmonisation activities and as a source of revenue. Ensuring a coordinated response around compliance and consistent guidelines for requirements on manufacturers is key to ensuring ongoing funding from these critical revenue streams.

Recommendation 2.2: Increased Pharmacovigilance Activities

Under the guidelines of the EAC, import fees are used by agencies for market surveillance and pharmacovigilance. Every NMRA expressed an intention to scale up their pharmacovigilance activities in the future. A common theme in our recommendations for the EAC-MRH is around transparency, and this was an area where pharmaceutical partners reiterated a particular request for visibility over fee use. Some even expressed a willingness to pay for additional pharmacovigilance activities, provided that there is clear line of sight over use of proceeds. Companies bringing products to EAC markets are beginning the request evidence for market surveillance activities and an understanding of the services that are supported by those fees.

Insights from Financial Modelling: Under our conservative financial modelling assumptions (2% growth in revenue from imports, no government or donor funding, and a 5% uptick in the number of different drug applications to the EAC as a whole) the EAC NMRAs as group will generate US$ 6 million in incremental profits by 2025 that could be spent on scaling up pharmacovigilance activities.

Besides pharmacovigilance being responsible for monitoring the safety of medicines in normal clinical use and during clinical trial, pharmaceutical companies can view this as a way of eliminating unfair competition from illegal and unregistered drugs. In recognising the importance of this activities, some of the larger international pharmaceutical manufacturers are willing to support the agencies to effectively carry out pharmacovigilance. This is in their interest, as counterfeit and sub-standard products damage both their profits and their reputation. The drug manufacturers are driven by revenues and profit from the sale of products therefore, this activity could be viewed as a way of promoting sales of their products. However, for the big pharmaceutical companies to pay a fee to support pharmacovigilance, the regulators need to demonstrate their ability to carry out pharmacovigilance effectively. This includes having full time resources in the field assessing the drugs in the store and creating awareness to the public to avoid unregistered drugs.

Key Point:
All NMRAs want to increase pharmacovigilance activities. Big pharma could pay for this.

This raises the question of NMRA capacity. In most NMRAs, there are very few employees that have been assigned to pharmacovigilance specifically, and for example in Uganda the NDA seeks support from employees of the Ministry of Health. Pharmacovigilance is not a revenue generating activity, though as noted previously some pharmaceutical partners have expressed a willingness to fund this. However, whether a proportion of retention fees is explicitly or implicitly earmarked for pharmacovigilance activities, our modelling suggests that internal NMRA funding is sufficient, particularly given an increase in the number of products registered as a result of joint evaluations and joint assessments. This would increase further in the event of unilateral recognition.

Pharmacovigilance is an area where ongoing EAC cooperation will be valuable. Kenya is a regional centre for excellence in pharmacovigilance. NMRAs in the EAC are undergoing a shift from largely passive pharmacovigilance activities (i.e. case reporting) to active post market surveillance, developing a clear protocol for collecting samples, reporting to inspectorate, and investigations. Part of the challenge is raising public awareness of the importance of pharmacovigilance. We are encouraged by the move of Kenya's PPB in January 2016, announcing that it will soon release a code where Kenyans can send text messages and receive prompt and specific responses about drugs, including registration status and safety. This is important in the context of growing counterfeit medicines.

While feedback from NMRAs and other stakeholders in the medicines regulatory process is that the likelihood of an increased allocation of public funds to NMRAs from EAC governments is low, one area of particular focus for the allocation of public monies is pharmacovigilance. This is a public good, but offers more limited direct revenue opportunities for agencies themselves. As noted, we believe that NMRAs have the capacity to self-fund these activities and pharmaceutical partners may support this, but NMRAs may also seek to access support from national governments.

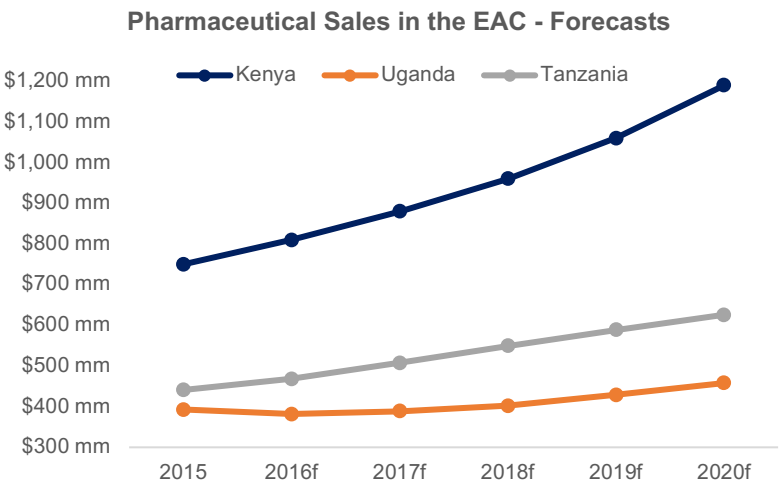
Case Study: Pharmacovigilance in the EMA

The EU pharmacovigilance system is one of the most comprehensive in the world, following new legislation that was adopted in 2010. The system aims to promote proactive risk management, as well as strengthened transparency, communication and patient involvement.

The model is directly relevant to the EAC as the Member States drive the EMA pharmacovigilance system. They provide much of the resource and knowledge for assessing signals of possible emerging side effects and take the lead in evaluating and analysing data when a safety issue is assessed at a European level. They maintain the inspectorates that ensure that medicines marketed in the EU are manufactured appropriately and are of suitable quality, and that the pharmacovigilance systems of industry are working as they should.

To ensure efficiency and alignment in member state activities, the EMA itself acts to coordinate activities and provide support to the Member States and industry. However, the responsibility for carrying out the inspections rests with the national regulatory authorities.

Recommendation 2.3: Using Data to Improve Market Attractiveness



A precursor to making the decision to enter a regulatory market is establishing whether that market is a viable commercial market. However, a critical nuance to that is that in their decision making, pharmaceutical companies often may not have accurate, or any, information about the market for a given drug in East Africa. The availability of accurate data on both the need for and the use of therapies in LMICs is increasingly a focus for donors and pharmaceutical companies, recognising that market uncertainty makes the decision on whether to enter a market much harder. It also obfuscates pricing decisions and even, the decision of whether or not to commercialise a particular product.

As well as being a significant driver of revenues, the collection of import duties has the additional benefit of providing some data on the current healthcare market within the EAC, data which is valuable market information. While the driver of a decision whether to register and import a product into EAC countries is predominantly commercial, and the economic and commercial attractiveness of the EAC largely outside NMRA control, NMRAs can provide clarity over at a subsection of the healthcare market (those products that are imported), which is a valuable indicator of potential market attractiveness to market entrants. This value to pharmaceutical partners derives from the value of additional market information when judging the attractiveness of a commercial opportunity. There is very limited evidence to either prove or disprove the pervasive belief that there is a limited market for pharmaceutical products in Africa. There is a pressing need for data around markets which have not

been well characterised for the pharmaceutical industry thus far. There are some relatively narrow silos where quality data does exist, but these tend to be confided to a particular country (e.g. Zambia) or product area (USAID-funded HIV-AIDS programs). There is a clear need for a robust set of data across products and countries, in order to inform pharmaceutical decision making processes. Higher market uncertainty increases the risk of market entry, and thereby reduces the incentive to enter a market. Data surrounding the EAC markets is very poor, and regulatory agencies can play a role in mitigating this.

Key Point:
Commercial viability is a precondition to enter a market. But many international manufacturers simply don't have sufficient market information to judge that.

While regulatory agencies can't create a commercial market where there isn't one, they can reduce the informational barriers in pharmaceutical companies' understanding of what commercial market there might be. The established regulatory agencies (Kenya, Uganda and Tanzania) currently maintain data on imports for tariff purposes. This provides at least an understanding of the existing market for a product, and the potential number of competitors. Providing a collated and sanitised version of this information to pharmaceutical companies will contribute to their understanding of the potential of the EAC as a market, and inform decisions about whether there is a commercially attractive market in the EAC. The work ongoing with Trade Mark East Africa and UNIDO has the potential to make a valuable contribution here. We would recommend that as that process evolves, the implementing team should bear in mind the value of the information they are collating to both regulators and the broader healthcare industry.

Ultimately pharmaceutical companies have a fiduciary obligation to their shareholders to pursue commercial opportunities. While many have some philanthropic or Corporate Social Responsibility (CSR) programs, these are not the core business focus. This means that any application for a new product within the EAC must occur within the context of an attractive market for commercialisation. Many companies have found ways to be successful in the past, and rapid growth in EAC countries will increasingly contribute to that success. However there remain challenges in commercialising in EAC countries meaning that in the absence of a clear commercial incentive, manufacturers simply do not prioritise allocating resources to accessing those markets. While the NRMAs cannot change the size of the market, they can reduce the friction costs for registration which in turn increases the attractiveness of registration.

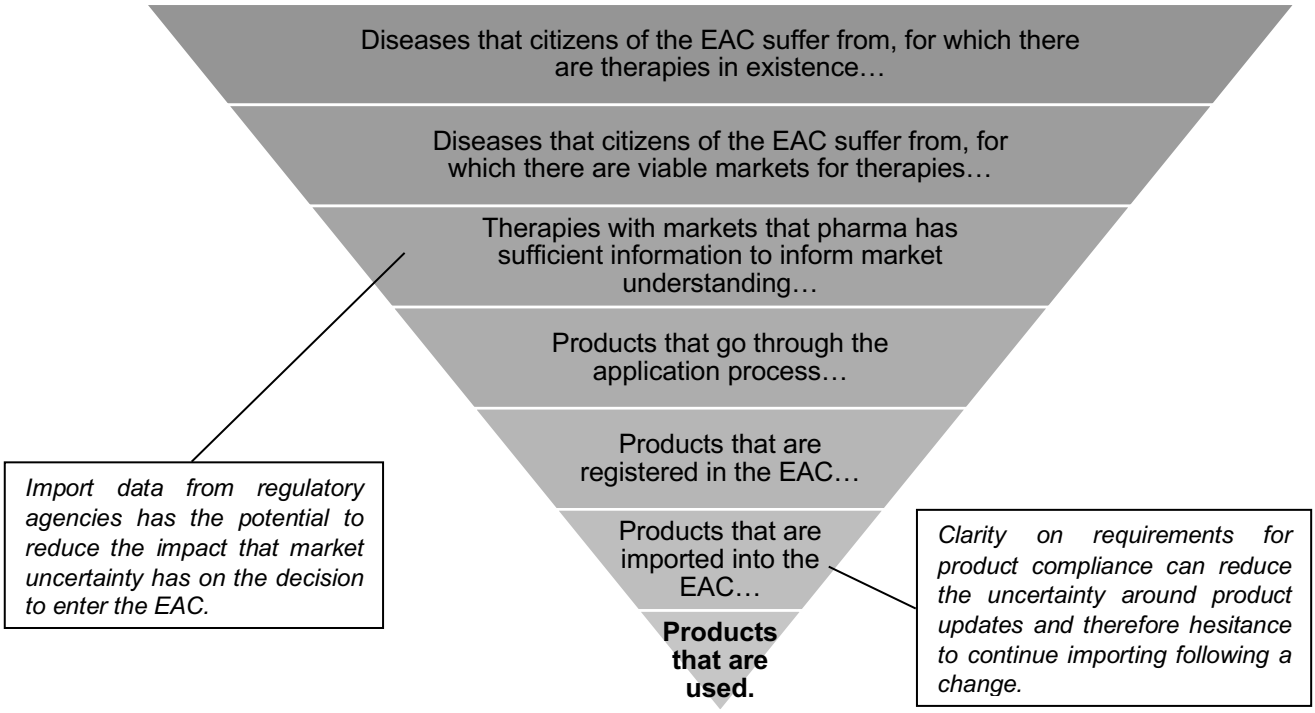


Table 8: Technology – Information Management Systems in the EAC

The EAC community and the NMRAs recognize the importance of Information Management Systems (IMS) in improving medicines regulation in the region and supporting the implementation of the EAC-MRH Project. Regulation of medicines involves documentary assessment of product information, inspection of manufacturing facilities, control of clinical trials, licensing of medicines outlets and post-marketing controls. These technical aspects of medicines regulation need to be supported by robust IMS. The NMRAs utilize technology to connect the regional offices to the head office. However, this system has not been linked to the other NMRAs. Most of the processes remain manual. As the initial step all the NMR s are expected to install a fully functioning system that could be linked to the other NMRAs in the later stages of harmonisation.

Implementation status at the NMRA level is as follows:

Uganda	Uganda's NDA started implementation of IMS in 2015. At the moment the user test acceptance has been completed and data entry is almost 70% complete. Training of the senior managers and Heads of Department was carried out in early 2016 while piloting the system to key stakeholders was started in June 2016 and is ongoing. The IMS is expected to be launched later in the year after the completion of stakeholder training.
Tanzania	The common IMS is fully functional. The web portal for import and export of products (Foods, Drugs, Medical Devices and Cosmetics) has been functioning since July 2015. GMP and premise registration module for the web portal have also been finalized and is live. The TFDA Laboratory Information Management System (LIMS) went live in May, 2016. The eCTD module is not yet developed.
Kenya	The system has gone live internally and externally. The Pharmacy & Poisons Board is currently working on integrating the system with Banks and the Kenya National Electronic Single Window which is in its final stages. All their modules apart from import and export have gone live and all process has web portals for external stakeholders to make applications.
EAC Secretariat	Development of common IMS at EAC Secretariat is at 60% of design, key modules are complete and Document Management System is being finalized to support electronic submission. User test acceptance will be carried out from September 2016 and is expected to last for a month. Regional IMS is expected to be launched during the EAC Head of State Meeting in November 2016.

Conclusions: Maintenance

The original terms of reference for this project define in their scope a focus on registration fees as the dominant source of revenues for NMRAs in the EAC. However, as this section establishes, a narrow focus on user fees may undermine the ability of NMRAs to act in the public interest, as they are incentivised or even forced through financial necessity to prioritise new drug applications that pay sizable fees, and the need for rigor is directly contrary to the brevity of application processing. In many other parts of the world, regulatory agencies rely heavily on public funds to mitigate this tension. Feedback from NMRAs has consistently emphasised that within the EAC countries it is not considered either likely or politically viable that national governments will offer increased budgetary support to medicines regulatory agencies. However, as this section shows, a move towards mutual and even unilateral recognition of product registrations across the EAC will contribute to NMRA financial sustainability through an increase in ongoing revenues that are both more profitable and more sustainable (lasting many years, as opposed to just one up-front payment).

There are steps that NRMAs can take to support and even encourage ongoing profits from imports and retention fees. While they cannot directly influence the commercial viability of their markets, they can provide market information to reduce uncertainty about these markets, while also ensuring that the ongoing compliance requirements for products that are already registered is as clear as possible. Given the relative importance of maintenance fees for ongoing agency profitability, these recommendations are relatively low hanging fruit for EAC NMRAs to support their own financial sustainability and as such ongoing harmonisation activities.

International Harmonisation Initiatives

Initiative	Aims	Member Countries	How Far Along	Responsibilities and Allocation Mechanism	Acceptance Mechanism	Smaller Members
East African Community Medicines Regulatory Harmonisation (EAC-MRH)	Establishment of a framework for joint assessment and approval of medicinal product applications for registration and inspections of medicine manufacturing sites, and to ensure that these assessments are integrated into national regulatory decision-making	Burundi, Kenya, Rwanda, Tanzania, Uganda, Zanzibar	Launched in 2012; joint assessments, joint evaluations with all regulatory processes are administered at the national level	Joint Assessments and Joint Evaluations alongside national registration and GMP inspections procedures	Issue opinion, final national registration decisions are the responsibility of individual agencies	Rwanda and Burundi don't have autonomous medicines agencies, mentoring relationship with Uganda
European Medicines Agency (EMA)	Single market in pharmaceuticals to allow free movement of products throughout the EU	31 EEA Member States	Fully harmonised	Centralised authorisation procedure by EMA for selected medicines granted by European Commission, National authorisation procedures for the rest; EMA responsible for coordinating GMP inspections	Full recognition of centrally authorised medicinal producr and GMP inspections	N/A
African Medicines Regulatory Harmonisation (AMRH)	Development of registration and regional regulatory platform on which to build African medicines regulatory capacity (common processes and frameworks)	54 AU member countries	Programme is being implemented through regional economic communities (RECs) in collaboration with partners (AU Commission, Pan African Parliament, WHO, World Bank, Bill & Melinda Gates Foundation, DFID and CHAI)	N/A	5-7 RECs covering the entire African continent, single set of requirements, resource pooling and information sharing	N/A
SADC Pharmaceutical	Improvement of the quality, safety and efficacy of medicines circulating within the region, and	Angola, Botswana, DRC, Lesotho, Madagascar,	Harmonisation proposal finalised in	Joint procurement of quality essential medicines	N/A	Several countries use medicine registers of other

Initiative	Aims	Member Countries	How Far Along	Responsibilities and Allocation Mechanism	Acceptance Mechanism	Smaller Members
Harmonisation Initiative	establishment of a regional shared network system for regulatory authorities	Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Swaziland, Tanzania, Zambia, Zimbabwe	July 2011; initiative in progress			members, e.g. Seychelles uses Zimbabwean national register as their own
ASEAN Healthcare Integration	Development of common technical requirements for pharma product registration	Indonesia, Malaysia, Philippines, Singapore, Thailand, Brunei Darussalam, Myanmar, Cambodia, Lao PDR & Vietnam	Implemented Common Technical Dossier (CTD) in 2009; Mutual Recognition Arrangement on GMP inspection signed by Indonesia, Malaysia, Singapore and Thailand in 2010 and implemented in 2011	Malaysia & Singapore Chair of GMP inspection taskforce	All ASEAN countries accept the CTD, even though some of the individual ASEAN countries have their own drug registration formats.	
ZAZIBONA Collaborative Medicines Registration Process	Development of Collaborative Medicines Registration Process	Botswana, Namibia, Zambia and Zimbabwe (process may be extended to include participation of other SADC Member States)	Process approved by the SADC Ministers of Health 12 Nov 2015	Collaboration between members	Issue opinion, final national registration decisions are the responsibility of individual participating authorities	

Theme 3 Governance & Capacity

EAC NMRAs have undergone a period of considerable capacity building in the past four years. However, all NMRAs express a desire to continue this development, both in terms of ongoing harmonisation activities and internally. While none of the EAC NMRAs have a legally autonomous framework in their member states, the need to legislative change is particularly apparent in the cases of Rwanda and Burundi. In these countries, the Ministry of Health does not charge for registration of medicines, and therefore regulatory activities rely on public funds for budgetary support. A regulatory agency that was able to charge fees would enable hiring of new staff, and promote some independence and autonomy in regulatory functioning. The Rwanda and Burundi ministries are prohibited by law from levying fees for medicines registration, which is an obstacle to a fully harmonised process. It is the national prerogative of Rwanda and Burundi how they structure future NMRAs, and this may be either mimicking that of their EAC partners or an alternative, complementary system akin to the Seychelles in SADC. Thus far, prohibition from collecting fees has hindered development of the NMRAs in those two countries, and if full harmonisation with similar processes were intended, legal review would be just one aspect of the transition for Rwanda and Burundi.

Governance is relevant both for individual NMRAs, and at the EAC level. Currently the EAC Secretariat does not have established sources of funding, process, budget, or protocols. How responsibilities are managed between the national and the regional level will depend on the relative strength of the institutions. In the long run, it is important that a credible overarching body is established to preserve the integrity of the EAC-MRH project over time in a context of changing individuals and politics at the national level. However, this has yet to be established and harmonisation activities remain very much the prevue of the member NMRAs.

Case Study: Historical Precedent for Legal Harmonisation in the EMA

The vision for the EMA was set up in 1995 with funding from the European Union and the pharmaceutical industry, as well as indirect subsidy from member states, in an attempt to harmonise (but not replace) the work of existing national medicine regulatory bodies. In this, the structure of the agency is the most similar to what the EAC is trying to achieve. The intent behind the creation of the EMA was to reduce the €350 million annual cost drug companies incurred by having to secure separate approvals from each member state. The EMA is distinguished from other national regulatory agencies in that it operates as a decentralised scientific agency (as opposed to a regulatory authority). More specifically, it coordinates the evaluation and monitoring of centrally authorised products and national referrals, developing technical guidance and providing scientific advice to sponsors.

The centralised procedure allows companies to submit a single application to the agency to obtain from the European Commission a centralised marketing authorisation valid in all EU countries and the European Economic Area states (Iceland, Liechtenstein and Norway). The centralised procedure is compulsory for all medicines derived from biotechnology and other high-tech processes, as well as for human medicines for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases, and for veterinary medicines for use for growth or yield enhancers. As a result, the majority of genuinely novel medicines are authorised through the EMA.

LONG TERM VISION: Clear Governance & Centralised EAC Coordinating Body

Due to the process of national bodies moving towards a regional regulatory system, the EMA is the most comparable model for EAC governance. In the EMA, an overarching body acts as a coordinator to decentralised regulatory activities occurring in national agencies, and therefore were this structure to be translated to the EAC, it would still require some responsibilities vested in the EAC. Currently there is no regionally mandated registration body, and enforcement of drug standards and imports remains the prerogative of the NMRAs. The EAC does not have its own income source, and therefore there is a need for a clearly defined allocation mechanism, not only of fees but also of responsibilities. The onus rests on the NMRAs to establish exactly what responsibilities should remain entirely at the national level (and hence see fees paid directly there), and which could become purview of the EAC coordinating body. As noted previously, in the event of a genuinely harmonised regulatory system (the current joint evaluation process is not seen to be sufficient by pharmaceutical partners), there is a clear willingness from pharmaceutical partners to pay incremental fees, if associated with a truly harmonised process, and even more so if this led to faster review times. This incremental fee could be used to finance the development of a centralised EAC Secretariat. Going forward, the NMRAs and the EAC

must work together closely to agree predefined allocation of roles and responsibilities. While the appropriate allocation of fee revenue will be a consequence of that, we anticipate that the majority of activities will occur and be funded at the national level, and EAC responsibilities will be limited to coordination, and therefore require a more limited permanent secretariat.

Insights from Financial Modelling: Our modelling suggests that the EAC coordinating body could certainly be financed by incremental fees in the event of truly harmonised regulatory system. A relatively small 10% increase in total registration and GMP inspection fees would allow the coordinating body to generate revenues of US$ 10 million by 2025.

As the harmonisation project evolves the EAC will be required to play a coordinating role, managing the allocation of applications to NMRAs and ensuring complementarity between member state activities. This means that there is a strong organisational onus on the EAC secretariat around the planning of activities, clear notice for meetings, agendas, and close communication with the NMRAs. To achieve this, the EAC will need to build out a dedicated team (potentially with some staff available 365 days per year), and in developing this will need to conduct a series of candid discussions with the NMRAs about how to define responsibilities and operate solutions.

The EAC will require funding in order to develop an independent function as the coordinating and oversight body of the harmonised region. This is an operational challenge, in that fees cannot be collected by the EAC unless there is a central regulatory body (EAC Medicines and Food Safety Commission) that is functional. Medicine registration is a legal process and only an entity that has legal powers to handle confidential information from the manufactures can receive documents and take fees. Currently this function can only be carried out by National Regulatory Authorities (NMRAs) which are established by law in their respective countries. There is a need for a law that establishes an institution within the EAC structures. Upon formation of this institution there will be need to capacitate it to take up the role. This will however take time to establish.

There is reticence among stakeholders in the EAC-MRH project more broadly to see an additional body or oversight structure created within the regulatory bureaucracy. While some have expressed an ambition to see some form of agreed EAC allocation mechanism, whereby pharmaceutical companies apply for EAC approval, and an EAC body acts in a similar way to the EMA to allocate the review process to an implementing national agency, this will require a change in the legislation of all EAC countries, and is not seen as either desirable for others or politically viable for most.

Key Point:
Harmonisation requires a legal framework with an operational body at the EAC level.

This balance, between an unwillingness to endorse another regulatory structure and the need for an overarching body within the EAC to ensure coordination and long term sustainability is at the heart of governance for the EAC going forward. The question of how this should be resolved is beyond the mandate of this study, but if the benefits of harmonisation are apparent to manufacturers, we are assured of a willingness to financially support it. It is our view that the EAC has a critical role to play, and politically given the emphasis on harmonisation more broadly in the region, can be a credible body in this regard.

IMPLICATION: Durability and Sustainability Beyond Individuals

For sustainability, it is necessary for institutions to be self-financing, and to endure beyond individuals. We are confident that the NMRAs with the appropriate structures can move to financial sustainability. However, in order to ensure the longevity of the MRH project, this requires an additional investment into the establishment of credible institutions that can endure beyond the individuals currently involved in the EAC-MRH. It is our view that the establishment of some separate EAC body is necessary to achieve this in the long run.

Implication 3.1: Need for Some Ongoing EAC Institution

For the long term durability of the EAC-MRH project, some overarching body is necessary to both coordinate activities and manage conflict between members. Currently activities are distributed into national responsibilities, whereby the Uganda NDA hosts GMP activities, Tanzania FDA takes the lead on screening of new product applications, and Kenya's PPB coordinates information systems and pharmacovigilance. While each of these NMRA's leadership in their respective areas is to be commended, without an overarching political

mechanism, it is not clear that long-lasting harmonisation can be sustained. With a national hosting agency, it is possible that in the future the process may become politically and personality driven.

The EAC Secretariat is ultimately a political institution and has the ability to demand responses from NMRAs. Without this oversight of national activities, the EAC regulatory system as a whole can become vulnerable. While feedback from NMRAs is that in the long run the preferred model is that of the EMA, whereby an overarching body acts as a coordinator to decentralised regulatory activities occurring in national agencies, this still requires some responsibilities vested in the EAC. Currently there is no regionally mandated registration body, and enforcement of drug standards and imports remains the prerogative of the NMRAs. The EAC does not currently have its own income source, and therefore there is a need for a clearly defined allocation mechanism, not only of fees but also of responsibilities.

Implication 3.2: Ability to Interact Internationally & Access Funding at EAC Level

Recognising that the EAC harmonisation project occurs within the context of harmonisation globally, the development of an independent EAC body is also important for the ability of the EAC to interact with other initiatives internationally and even access funding as a group. There are options for regulatory agency financing through accessing the capital markets. As a possible addendum to this project, LHGP could do an initial scoping of potential mechanisms to leverage the future revenues of the EAC and allow for the release of funds up front for capacity building and transition, smoothing revenues alongside agency costs. This would be a very high level analysis but may serve as a starter point for work considering any such option.

> ***Key Point:***
> *A functional and independent EAC body can coordinate activities both within the EAC and with international bodies, including accessing incremental funding for the group.*

TRANSITION RECOMMENDATION: Coordination at National Level

However, the EAC as an independent institution does not currently exist. At the national level, there is extensive political goodwill for harmonisation across the political spectrum, and NMRAs can capitalise this to extend the harmonisation process while also acting to support it by taking responsibility for different areas. Full centralisation is not always necessary for effective regulatory functioning, indeed, in SADC one of the NMRAs acts as secretariat in turn.

Recommendation 3.1: NMRAs take ownership of different areas

In the near term, the harmonisation program can be institutionalised in by continuing the existing hosting of responsibilities by NMRAs:

- **Kenya:** Health Systems and Pharmacovigilance
- **Uganda:** GMP
- **Tanzania:** Screening new drug applications

Furthermore, while previously we had assumed the need for an EAC allocation mechanism, further discussion with partners has led us to believe that this is unnecessary. With the most important factor for registration for companies being time to market, with mutual recognition review times will become a way of ensuring relatively even distribution of applications. Those agencies that are able to review more applications will do so, until such point as their processing time becomes disproportionately high. The processing time will serve as a market distribution mechanism, as companies will take their applications to those agencies where they see the fastest access to market.

Conclusions: Governance

Governance is critical but in many ways the most complicated of the themes described herein because developing a sustainable credible structure is more a question of politics than of finances. There is a chicken-and-egg scenario, whereby the establishment of a credible structure will allow the EAC as a whole to access increased funds for sustainability through incremental fees and funding at a regional level. However, the EAC needs these funds in order to implement a credible structure. With a further year of donor support, we would emphasise the importance of ensuring these structures are in place before July 2017. We are confident however that if this can be achieved, ongoing revenues from the regulatory process can adequately support it.

Theme 4 Developing EAC Specific Capacity

The creation of the EAC and the MRH process, as well as the considerable investment and support from donor and international regulatory partners has gone a long way towards providing structure and clarity in the registration process for new products in the EAC. Over the last two years the EAC and partners have established a multitude of guidelines across healthcare. While there remains room for improvement, it is important not to disregard the considerable progress that has already been made. Pharmaceutical partners express a willingness and an enthusiasm to continue to work with EAC regulators, particularly on innovative products that do not have heavily-reviewed dossiers. As business models shift within the pharmaceutical sector to see LMICs as commercial markets of their own right, rather than secondary to developed markets, there is a complementary growth in products that target LMIC countries as their primary geographies. African regulators, and the EAC in particular, therefore need to develop regulatory expertise that can support and accommodate this trend. Through the recommendations outlined above, the EAC has the opportunity to rationalise their regulatory process in a way that both provides long term financial sustainability to the NMRAs, but also supports bringing products to market that focus on EAC citizens as a first priority. SRA-expedited review means that NMRAs can focus their review activities on quality control and suitability to the local market. For those products that are entirely novel, they can work with pharmaceutical companies to build expertise at the forefront of healthcare that is targeting Africans first and foremost. One of the key motivations of the EAC-MRH is the critical need to produce creative, African sourced solutions, responsive to the particular needs of African people. While we believe the EAC-MRH will encourage local production of medicines, much of this innovation would occur in partnership with other developed and emerging economies.

LONG TERM VISION: Developing EAC-specific Expertise

The EAC can be a market leader in the development of African regulatory expertise for novel products targeting Africans. Drug companies are increasingly becoming more comfortable with the concept of tiered pricing and the pace of patent expiration in Western markets only continues to build the opportunity set for EAC governments to bring new generic drugs into their region, particularly around the growing challenge of non-infectious diseases. This offers significant potential for improved availability of medicines in the EAC and the opportunity to leap-frog technology and systems. For pharmaceutical companies, there are significant benefits from greater economies of scale through pooled procurement, faster patient access to innovative new products, and patients can be treated at lower cost.

Despite a clearly defined harmonisation schedule and process, and an enthusiasm and political will around medicines regulatory harmonisation at the top levels of EAC government, politically there is still competition between countries, in particular as it concerns the development of NMRA expertise. Previously we had considered whether a structure whereby each NMRA would specialise in a particular disease or product area, and therefore become the go-to agency within the region for a particular product. However, this is neither politically viable nor practicable within the EAC without a clear and strong allocation mechanism. There is precedent for this in other countries, but it is not the only approach.

Feature 4.1: African Regulators pooling NMRA expertise

An alternative is to pool EAC NMRA expertise to create an African Regulators team, which could overlap in membership with the WHO or other SRAs who are willing to provide technical support. Continuing the existing joint review and learning trips, multinational corporations would also support the process, but the engagement would be one of teaching rather than examination. Pharmaceutical companies have expressed a willingness to engage in this. Groups like the Developing Country Vaccine Manufacturers Network could arrange learning trips to enhance cooperation between EAC regulators and manufacturers outside Northern America and Europe. This would also allow for the development of new skills in frontier healthcare products like biosimilars. The areas of vaccines and biologicals are one where the EAC has seen a clear development in expertise following capacity building with the WHO and SwissMedic, whereby NMRAs received guidance and access to products that were previously relatively foreign. There remains considerable room for other organisations to assist in terms of capacity building, and pharmaceutical partners have expressed a willingness to engage further in sponsored training and management.

A key component of capacity building is the ability of different NMRAs in the EAC to leverage each other's expertise. This will require information sharing of techniques, historical evaluations, and issues encountered. Information sharing is also pertinent to the broader market, whereby investors, pharmaceutical companies, donors and other global health stakeholders can gain a better grasp on the needs, sensitivities, and commercial attractiveness of the EAC as a region through the availability of regulatory data.

Case Study: EMA Strengthening Interaction with Academia, Innovative Medicines Evaluation

The collaboration between EMA and academia is longstanding. Many representatives from the academic sector contribute their expertise and knowledge as experts in the evaluation of medicines, ensuring that regulatory developments in the evaluation and monitoring of medicines are keeping pace with the speed of scientific development. Simultaneously, interaction with EU regulators and a better understanding of the regulatory environment can help academia translate their discoveries into patient-focused medicines.

The main focus of the collaboration is to development a new trans-disciplinary model enabling full deployment of the personalised medicine paradigm in Europe.

The framework is set to be finalised and adopted by EMA Management Board by the end of 2016, with its initial implementation phase starting at the beginning of 2017.

Feature 4.2: Regional Medical Research Institutes

Many regulatory agencies globally require a clinical trial in a representative population. Development of capacity to host and run clinical trials aligns with the themes expressed here of developing EAC-focused expertise. More effective regulatory agencies and increased capacity in novel areas that directly target EAC citizens will also increase the role of Medical Research Institutes in the EAC. Linkage with medical research institutes in the region will become increasingly important, as primary data from these sources will be of greater value than that of trials elsewhere. This development of local skills and expertise must however occur in the context of pooling of clinical findings, and therefore the capacity to "passport" that data across regulatory authorities is of key importance. In this regard groups such as the European and Developing Countries Clinical Trials Partnership (EDCTP) can be very helpful in supporting more rigorous and locally relevant clinical trials.

This set of recommendations is centred around a theme of building out regulatory technical capacity through eliminating replication in regulatory activities internationally, and expanding capacity for locally-focused expertise. These changes will contribute to the development of better local pharmaceutical expertise, further developing the role and influence of EAC Medical Research Institutes, and therefore the profile of EAC healthcare more broadly. This work can also seek to leverage the Product Development Partnerships (PDP) such as the Drugs for Neglected Diseases Initiative (DNDi) who target diseases that affect EAC citizens. Many of these groups already work closely with EAC regulators on establishing the regulatory pathway for entirely novel compounds. Building out the Medical Research Institutes and the NMRA capacity to adequately handle these compounds will both support the provision of new and life-saving products for the region, as well as incentivise further innovation targeting it.

IMPLICATION: Increased Innovation in Products Targeting EAC Citizens

With a harmonised and effective regulatory system, there is the potential for EAC healthcare to leapfrog that of developed countries. The increased knowledge and influence of local Medical Research Institutes, as well as an EAC specific capacity within NMRAs, developed because of an ability to leverage the activities of other SRAs globally and each other, will contribute to an environment that supports innovation in products targeting EAC citizens. National Sovereignty in NMRAs can be preserved as NMRAs may choose what to specialise in and which kinds of products to support depending on national health priorities.

Distribution for medical products is also a major issue, and therefore regional hubs can serve as an important focus in the region. With a growing number of international pharmaceuticals focusing on Africa, there are also questions around the attractiveness of the market, profitability of market entry, lengthy registration process and uncertainty about regulatory process. The EAC-MRH is an ambitious endeavour to streamline this process and hence increase the attractiveness of East Africa for future registration of new medicines, thereby improving the

price and accessibility of life-saving drugs to East Africans. To tap into the growing healthcare innovation worldwide, policies and procedures need to be put in place that ensure regulatory approvals process are streamlined substantially

Implication 4.1: Neglected Diseases

The development of EAC specific capacity in the NMRAs is particularly relevant for neglected diseases. We would note that regulatory process alone cannot incentivise innovation in uncommercial markets. However, there remain a series of tools whereby regulators can support innovation in these areas, such as Priority Review Vouchers (discussed more extensively in our earlier report). To ensure access to products for neglected diseases and areas, such as paediatric formulations, NMRAs can work closely with donors and groups like DNDi.

It is important to distinguish between those drugs that are registered; those that have a market that would be registered *if the process was easier*; those that don't have a commercial market so regardless won't get registered. Even the most streamlined regulatory process won't incentivise registrations for neglected diseases in the absence of any other mechanism or donor support. We have previously outlined some potential mechanisms that over time the EAC may wish to consider in order to support the advancement of certain healthcare priorities. This is beyond the scope of our project, but it is important to highlight the role of other mechanisms in the healthcare financing that can be used to support specific aims, and potentially to overcome the hurdle of commercial attractiveness for pharmaceutical companies.

Implication 4.2: Local Manufacturing

While local manufacturing is currently supplying a relatively small proportion of the overall EAC healthcare product needs, EAC harmonisation will be supportive of both manufacturing in the East African Region and across the African continent. Building out this local industry is critical to allow East Africa to effectively compete with current Indian supply, as well as future supply from other African markets such as Ethiopia and Nigeria both of which have ambitions to build strong domestic pharmaceutical sectors.

TRANSITION RECOMMENDATION: Remove Barriers to EAC Innovation

Recommendation 4.1: Waiving requirement for product to be registered in country of origin

Currently, NMRA and EAC registration process requires international applicants to have registered the product under review in the country of origin before beginning the registration process. While this requirement can be waived if a suitable justification case can be made (for example, the lack of prevalence of a certain disease in country of origin), it still contributes to a delay in beginning the registration process. This requirement dis-incentivises innovation that specifically targets East African countries. Through the resource savings of SRA-expedited review, NMRAs can reallocate agency expertise away from review of well-established or well-reviewed drugs towards novel compounds that target the citizens of EAC countries. Historically NMRAs have used the requirement for country of origin registration as a means to build capacity and build regulatory expertise by undergoing a full assessment of the regulatory file that has already been approved by an SRA, and in doing so learning more about the review process. However, recognising the skill and capacity of Kenya, Uganda and Tanzania now, in the interests of public health of EAC citizens (faster access to life-saving medicines) and in expanding NMRA capacity into newer areas, this requirement now places an undue delay on access to medicines within the EAC. We note that while companies can be issued an exception if the disease is not prevalent in their countries, but feedback from partners indicates this takes a while to process. We would recommend reducing this requirement and vastly simplifying the process for waiving it.

Recommendation 4.2: Products for Joint Evaluation are set by NMRAs

Over the course of the EAC-MRH project, the Joint Evaluation sessions and WHO-led Joint Assessment program have offered a temporary solution to provide assistance in some countries who do not currently have the capacity to do a credible evaluation themselves (such as Rwanda and Burundi). In these cases, WHO prequalification (PQP) may be viewed as a temporary proxy, particularly where international donor purchasing agencies are planning on purchasing sizable volumes for use in-country. Initially all Joint Evaluations were

conducted focusing on WHO priority medicines. However, the WHO's priorities do not necessarily align with national priorities, and therefore we would recommend that as the ownership of the EAC harmonisation process moves to the NMRAs themselves and donor funding diminishes, all products become eligible for joint evaluation and NMRAs are able to set the agenda for what should be evaluated.

One option could be for the NMRAs to jointly conduct a rationalisation of the roster of dossiers already registered in EAC member countries, searching their databases to establish what products are common, and use those most common products as a starting point for start with them.

> *"WHO won't teach you how to evaluate **Viagra**."*
>
> *~ NMRA Staff Member*

Recommendation 4.3: Fast Track Review can be used to support *National* strategic health priorities

National sovereignty in healthcare regulation remains important, both politically and in terms of NMRA's ability to determine their own strategic priorities rather than being overly influenced by international focus. As previously highlighted, the single most important factor for pharmaceutical companies in the new product registration process is time for review. This means that NMRAs can use speed of review as a tool to support national public health outcomes and maintain national sovereignty. NMRAs can commit to an expedited review for products targeting certain conditions or disease areas in order to incentivise innovation in these areas. If each EAC member NMRA were to utilise this mechanism, it will lead to a natural competition between agencies, whereby pharmaceutical companies with products that target those priority areas will target those agencies with the shortest time to market. Agencies can leverage this to support national strategic health priorities and incentivise innovation and new product registration for those areas by committing to a fast track review. This may or may not have higher fees associated with it. Individual EAC countries can choose to prioritise applications for particular national health agendas, but the EAC as a whole will benefit through mutual recognition of review conclusions. In time, this may lead to a natural process of diversification in expertise between agencies. As previously illustrated, the regulatory body in a region has a powerful position in terms of its ability to support and incentivise innovation in priority areas. Fast track review is one such mechanism that has been used to great effect in other geographies – whereby therapies for specific diseases which the government sees as a priority to address in the near future are awarded expedited review.

Table 9: Healthcare markets in EAC Member Countries

	Kenya	*Uganda*	*Tanzania*	*Rwanda*	*Burundi*
Health Expenditure (% GDP)	4.5%	9.8%	7.3%	11.1%	8.0%
Health Expenditure per capita (US$)	45	59	49	71	21
Health expenditure per capita annual % change	1.0%	1.1%	1.1%	1.2%	1.1%
% Public	42%	44%	36%	59%	55%
% Govt Spending on Health	6%	24%	11%	22%	14%
Proportion from Donors	45%	46%	33%	38%	73%
% Out of Pocket Spend	45%	38%	33%	18%	20%
Healthcare Industry Size (US$ mm)	3,620	2,100	2,320		
Growth (US$ terms)	4.3%	(3.1%)	2.5%		
Growth (Local FX)	10.5%	9.0%	9.9%		
Pharmaceuticals Industry Size (US$ mm)	806	382	468		
Growth (US$ terms)	8.0%	(2.8%)	6.0%		
Growth (Local FX)	14.5%	9.3%	13.6%		

Conclusions: Developing East African-specific Expertise

The East African people have particular healthcare needs, and represent an important and growing market for pharmaceutical manufacturers. Increasingly the business model is transitioning from being one focusing largely on Northern America and Europe, with other nations as a secondary consideration, to more targeted and even personalised medicine, recognising the diversity in need and response between genders, races, age, and size.

In order to most effectively serve their citizens, and keep up with innovation, regulators need to continually develop and refine their expertise. While the EAC NMRAs have previously relied heavily on support from international partners for capacity building, they are now ready to move to a more independent approach, one that is more reflective of and responsive to the needs of their citizens. Harmonisation supports this, by allowing EAC NMRAs to pool their expertise and leverage each other's capacity, thus creating the space for increased specialisation outside existing areas. This process will contribute to a more influential and credible local medical research institutes and a greater ability to adapt to the changing healthcare needs of the EAC public.

Theme 5 Global Presence and Leadership

As the pioneering harmonisation initiative on the African continent, the EAC has a significant first mover advantage and can benefit from the potential of the harmonisation initiative to scale. With growing EAC credibility, other regions will look to the structure and leadership there as a model for harmonisation on the African continent. Despite strong population and industry growth rates, the African continent can still be viewed as a difficult market by international pharmaceutical companies – not least due to its relatively small size (though they recognise the growth potential) and need to interact with multiple agencies. In interactions with pharmaceutical partners, we have been struck by the fact that African regulatory teams are generally siloed away from the pharmaceutical companies' core market divisions, with many in leadership positions of international pharma simply viewing Africa as "terra incognita". The EAC Medicines Regulatory Harmonisation project has the potential to transform perceptions of the African market as a destination for pharmaceutical products. More broadly, the EAC project is part of a greater harmonisation trend and as such serves to benefit as other regions in Africa follow suit.

LONG TERM VISION: Harmonised African Continent

As previously mentioned, a critical component of the harmonisation project is that it is not simply an EAC initiative, but rather is a continental initiative. The move to MRH in EAC is part of a wider global trend. However, the EAC is a leader in Africa in this regard. Efforts are being made towards medicines regulatory harmonisation and regionalisation in sub-Saharan Africa. The African Union's African Medicines Regulatory Harmonisation Initiative has a regional economic community approach. The East African Community launched the harmonisation of medicines registration in its member states in 2012. A strategic business plan was developed for centralised registration, inspection and testing. A similar initiative was created in the Communauté Économique des États de l'Afrique Centrale. In the Southern African Development Community (SADC), a pharmaceutical business plan has been agreed to build capacity for less experienced regulatory authorities and to develop regulatory guidelines. The West African Union Économique et Monétaire Ouest Africaine established in 2006 a regional committee for veterinary medicines which has reviewed 21 regional medicines applications. The Union Économique et Monétaire Ouest Africaine started harmonising registration of human medicines by directive in 2010. However, to date, the harmonisation of medicines regulatory activities is not yet finalised in all sub-Saharan African regions due to the lengthy appraisal and long negotiating processes by stakeholders. Therefore, the work done by the EAC is pioneering and could define a path for future regulatory harmonisation efforts in creating a sustainable financing model.

Key Point:
Keep broader harmonisation context in mind to avoid having to "harmonise the harmonisers" in the future.

Feature 5.1: Feeding into existing Initiatives

While the MRH project is most certainly "made in East Africa", the rest of Africa will be looking to the East African Community, as the benefits of harmonisation, and the lessons learned in the EAC, can be applied throughout the continent. Global stakeholders support this initiative but it must be driven by the needs and demands of the East Africa Community countries themselves. From that platform, the EAC and partners can create a locally sensitive model to drive the broader availability of critical, life-saving medicines in the EAC and, through future harmonisation efforts, across Africa. While the EAC took time to write their own protocols, leveraging but not replicating those of ICH, other harmonisation initiatives can build off this work and for future regions the harmonisation process can be expedited compared to the history of the EAC. Ongoing EAC work should bear in mind the importance to be aligned with, and learn from, other regional initiatives, recognising that the ultimate goal is a harmonised regulatory process throughout the African continent. Keeping this in mind in EAC harmonisation is important in order to avoid having to "harmonise the harmonisers" at some point in the future.

Feature 5.2: Coordinated Epidemic Preparedness

The Ebola outbreak in West Africa demonstrated the critical importance of the ability of health systems to react at speed to an emergent threat. Epidemics can place extraordinary pressure on regulatory authorities as countries come under great pressure to approve products to tackle the epidemic, often whilst those products are relatively early in their clinical development pathway. As the World learns the lessons of the Ebola

epidemic, there is an increasing recognition of the critical role that the regulatory authorities play. This creates the opportunity for the agencies of East Africa to establish a common approach to potential emerging epidemics and to leverage some of the post Ebola capital which has been pledged to improve future preparedness.

This similarly highlights the importance of regulatory harmonisation and cooperation. Diseases do not respect regulatory boundaries. With urbanisation and globalisation contributing to the rapid spread of many vector-borne diseases (such as dengue, chikungunya, Zika and yellow fever), there are a number of emergent international initiatives attempting to respond to this undefined, future threat. Initiatives like the Coalition for Epidemic Preparedness Initiative will require in-county regulatory counterparts in the approval and deployment of products to respond to future epidemics, and the more harmonised and well established the regulatory approval processes are, the better the response. The EAC as a group can access funding to work with the global community on setting a precedent for regulatory cooperation and epidemic response.

In the event of an emergency outbreak, countries across the affected region will need to be coordinated in their response, requiring agreement on protocols for clinical trials and the registration of vaccines and medicines in advance. Data may be derived from diverse settings and the timeline is unlikely to confirm to standard procedure. Through our work on other initiatives, LHGP perceive a gulf between the theoretical regulatory coordination being discussed by donors and international regulatory bodies and the reality of regulatory epidemic preparedness on the ground. Emphasising the importance of African ownership of the regulatory process, this preparedness is critical to avoid a situation whereby international regulatory processes overrule local in order to ensure speed of response.

Similarly, Emergency Response, and the development of appropriate systems and protocols represents a target around which the different NMRAs can cooperate to establish common procedures without representing a division of finances or activities today. These processes can be extrapolated to existing drugs and vaccines in the future. The EAC-MRH project was funded at inception by international donors. Now however EAC member countries can take ownership of this process and remove the need for donors to play that historic role. This does not mean the end of EAC-donor cooperation, but rather a transition to a new relationship whereby the EAC can work with global donors and their different strategic priorities to push forward frontiers in healthcare. The Coalition for Epidemic Preparedness Initiative represents one such opportunity.

Key Point:
The threat of epidemics increases the importance of harmonised and effective regulatory bodies. The EAC can work with international partners to establish appropriate frameworks for epidemic readiness.

IMPLICATIONS: Setting a Precedent Across Africa

As the first regional harmonisation in Africa, the EAC can utilise their first-mover advantage to provide leadership and outreach across Africa, establishing precedent for Medicines Regulatory Harmonisation. Just as SADC has utilised the protocols established by the EAC, so other harmonisation initiatives can move quickly to follow suit. As the ultimate goal of harmonisation is across the African continent, these changes mean that perceptions of EAC specifically, and Africa generally, can shift towards an image of an attractive commercial market with credible health systems.

TRANSITION RECOMMENDATIONS: Establish Global Leadership and Presence

Recommendation 5.1: Work with Global Donors to establish New Frontiers in Harmonisation, for example the Development of a Framework for Epidemic Readiness

Following the Ebola outbreak in West Africa, there is an increasing awareness and focus on the need for strong health systems that are aligned across borders to rapidly and effectively respond to any future outbreak. Regulatory systems are a critical part of this. There are a number of initiatives ongoing, including the Coalition for Epidemic Preparedness, the Campaign for Epidemic Readiness, the work ongoing with AVAREF, and others. Within the EAC, and in particular Uganda, there is political appetite for quick response system, as East Africa does not want to be found unreactive and unresponsive in the event of another outbreak. These projects represent an opportunity for the EAC to work together with donors, accessing additional funds, to support the

development of a coordinated response to epidemics. Of course, these lessons are equally translatable to many other regulatory activities, and as such supportive of harmonisation as a whole.

Recommendation 5.2: Maintain Coordination with other Regional Harmonisation Initiatives

Regional harmonisations in Africa can leverage the work done in one region to support the harmonisation process in another. Through the coordination of The New Partnership for African Development (NEPAD), SADC and ZAZIBONA continue to work closely with the EAC. NEPAD and the WHO are among main drivers of Medicines Registration Harmonisation project in EAC. NEPAD plays a critical role in AMRH initiative by engaging with regional economic communities and other arms of African Union including the Conference of Ministers of Health and African Union Commission (AUC) as well as the Pan African Parliament (PAP) to further enhance political commitment and support for enactment of relevant policies and regulatory framework.

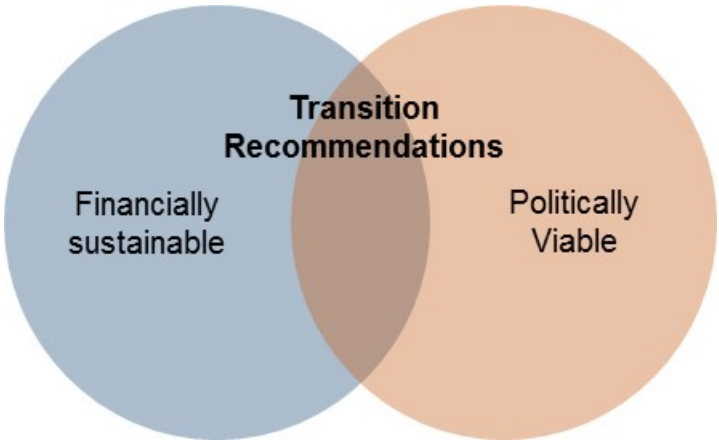
NEPAD acts to replicate the harmonisation process from the EAC to other regions in Africa. The success of EAH harmonisation is essential as this will guide harmonisation of other regions and later on Africa Medicines regulation and harmonisation. THE EAC can continue careful work with NEPAD and the ongoing input and cooperation with SADC, ZAZIBONA and others to ensure this process is as smooth as possible.

Conclusions: Global Leadership and Presence

With the addition of each new country and regulatory function into the harmonisation program, the scope of the project grows beyond the initial mission. Since inception, the harmonisation program has expanded to include other regulatory functions such as pharmacovigilance, and regulation of products such as medical devices and diagnostics. These areas may also be regulated at the national level by different regulatory agencies other than the ones currently actively involved in the harmonisation project. The inclusion of different areas of scope and countries increases the potential for harmonisation to be a win-win for the region, but also increases the complexity of achieving buy in from a larger group of stakeholders.

Political Stakeholders

As noted previously, the recommendations outlined in this report were developed with political viability in mind. Therefore, the long term vision represents the ultimate goal for the EAC and associated financial sustainability. Each transition recommendation is in effect a political roadmap towards that vision, taking into account what is politically viable compared to what may be ideal from a financial perspective.



There is currently an enormous amount of goodwill for the harmonisation process in Africa more broadly, and in the EAC in particular, from both national governments, donors and other international stakeholders. The pharmaceutical industry remains enthusiastic about the potential benefits of the process. There is however a time-sensitivity, as currently the EAC-MRH project rests on the cooperation and leadership of individuals, which is not sustainable in the long run. In developing these recommendations and as the NMRAs work together to further strengthen the harmonised EAC as an institution, it is important to bear in mind the buy-in and support of the three major groups of partners.

1. Industry

Revenues from user fees are driven by a supply of applications from pharmaceutical companies – this means they must buy into the value of registration in the EAC. There is a clear willingness in pharmaceutical companies to engage with the harmonisation process, not least because of the potential benefits of a streamlined regulatory system. However, this will only occur in the context of transparency and good faith. Not only does the EAC need to be supported with revenues of its own, in order to reduce reliance on donor funds, but equally both pharmaceutical companies and the NMRAs must be confident that this transference of wealth is being used in a manner that is contributing to the advancement of healthcare goals in the region. It is for this reason that the fee structure recommended by LHGP is to maintain fee payments to the NMRAs – but to ensure that the benefits of harmonisation are apparent to manufacturers. It will be necessary to secure support from the local pharmaceutical industry, via their industry associations and individual representatives, who will want assurance that this will not disadvantage them, the international pharma industry who will want to know that they are not being asked to take on a disproportionate amount of the cost and civil society, who will want to ensure that essential medicines ultimately do reach the last mile and in doing so have not become degraded or replaced with fake products.

2. National Stakeholders (NMRAs)

National sovereignty is paramount, and any recommendations that are to be viable need to be acceptable to the EAC NMRAs. Throughout this process, we have engaged continual feedback from NMRAs in order to be sensitive to the sovereignty of the national EAC states. Given the involvement of international donor partners, all guidelines and recommendations must be clearly developed in cooperation with NMRAs to preserve national sovereignty. Additionally, within each country there can be huge political interest and interference in the health sector, and therefore NMRAs must ensure that their processes are aligned with national health priorities, but sufficiently independent to act in the public interest without political interference.

3. Global Stakeholders

It will be critical to build consensus around the regional integration of the NMRAs. As with many of the other regional integration programmes underway with the EAC there will be resistance and a strong case must be

made of the benefits of this proposal. The alternative is that the plan moves forward without strong buy-in but the National groups will work to undermine the proposal for their respective benefit. At its heart, this is about securing support at the NMRA level, demonstrating how this will reduce risk of a failure and improve sustainability. We believe that with the solid financial plan outlined in this report this will be achievable.

The EAC MRA will require collaboration between national agencies, the cooperation of other public and parastatal bodies (those responsible for imports, distribution etc.) A key question for next steps is around the format for delivering the recommendations to the EAC, the NMRAs and other global stakeholders. LHGP look to the EAC Secretariat, the World Bank, and the NMRAs themselves for guidance on the appropriate forum for this.

Conclusion: Financial Sustainability in the East African Community is a Win-Win

It is a rare project that can genuinely bring benefit to all participating stakeholders without that value coming at the cost of other groups. Medicines regulatory harmonisation represents one such opportunity. We have outlined a series of transition recommendations in pursuit of achieving the long term vision of true harmonisation and in the process establishing the best model for sustainable financing. In finding the middle ground between political viability and financially optimal, it is important not to lose sight of the enormous opportunity to create a true win-win scenario for both manufacturers, regulators, policy makers and ultimately, patients.

A harmonised regulatory process will increase the quantum of new drug applications from the sub-optimal level of today, and ultimately support the development of the EAC as a regional hub for manufacturing, healthcare best practices, and a foothold for international companies looking to enter the African market. We have established the five key themes around which these recommendations are based, which revolve around building on the existing harmonisation activities and fee structure to move towards mutual recognition while revenues deriving from maintenance (retention fees and import duties) support ongoing profitability and financial sustainability. The introduction of a stringent regulatory authority expedited review has the potential to vastly supplement fee incomes while limiting strain on agency resources – we have been very conservative in our model with this, meaning there is considerable upside potential from this mechanism. We then considered appropriate structures for governance within the EAC, and how this relates to the development of EAC-specific capacity. Finally, we highlighted how the EAC can act as a leader for pan-African harmonisation, and engage with international partners on a new footing.

We now look to EAC stakeholders, and in particular the NMRAs, to move forward with implementation. These recommendations have been developed in partnership with the regulatory agencies and broader EAC partners, taking into consideration the views and incentives for each of the stakeholder groups outlined above. We hope that it makes some small contribution to progressing what we believe is an initiative with enormous potential, within the EAC and beyond. We look forward to seeing the East African Community Medicines Regulatory Harmonisation project continue to contribute to an effective and high qualify market for healthcare in member countries, and support the better health for EAC citizens throughout the region and throughout the continent.