Strengthening regulatory systems in LMICs

Improving the sustainability of the vaccine innovation ecosystem in Africa

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Disclaimer: This is a fast-moving area and the landscape is continuously emerging. This report should be read as correct at the time of publication.

Acknowledgements: The authors would like to acknowledge all those who contributed their invaluable insights to this report both via interviews and in writing.

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1. Executive Summary

The availability of safe and effective vaccines and medical products is increasingly a central concern for all governments and citizens alike. When a regulatory system performs well, patients and health systems may benefit from rapid and sustained access to high-quality, safe and effective products. However, when it under-performs, product availability is often delayed and costs to health systems, individuals and society are increased by the effects of substandard or falsified products. Despite marked progress in the past decade, in many resource-limited settings, there can be long delays for filing, approval and launch of vaccine and medical products relative to their introduction in high income countries.

Policymakers and non-governmental funders interested in increasing access to vaccines and medical products through the strengthening of regulatory ecosystems face complex decisions about how to allocate their funds, often without a comprehensive picture of needs and opportunities. The Wellcome Trust commissioned this report to provide an accessible and accurate overview of the current state of investment needs for regulatory ecosystems in Africa. The report looks at the regulatory lifecycle for vaccines – across the research and development, manufacturing, distribution and post-marketing and pharmacovigilance phases – as well as considering the issues for a wider set of medical products essential for the promotion of public health.

The content and recommendations in this report were generated through a literature review, informant interviews and consultation with expert regulatory professionals, global health practitioners and funders, with an emphasis on mapping the reach of existing initiatives already in place to strengthen regulatory systems in Africa and identifying any insights from selected initiatives on other continents. The information was organised along the regulatory lifecycle, to reflect the core regulatory functions as defined in WHO's code of Good Regulatory Practice, and to identify the operational needs of a regulatory system and the investments that would improve regulatory outcomes.

COVID-19 has brought to the fore the need for more reliable and timely supply of vaccines and medicines across the continent, prompting a resurgence of political support for local manufacturing. This in turn has raised awareness of the need for appropriate regulatory oversight. To-date only four African National Regulatory Authorities (NRAs), Tanzania, Ghana, Egypt and Nigeria perform as Maturity Level 3 agencies for

pharmaceuticals, a designation given by the World Health Organization (WHO) to acknowledge that a country has a stable, well-functioning and integrated regulatory system. Only Egypt has achieved a Maturity Level 3 for vaccine regulation of locally produced vaccines.

Despite significant accomplishments and progress forward in the last decade, major challenges are still faced by regulators in Africa:

- **Financing regulatory system strengthening at the national level is challenging** – not all NRAs in Africa are autonomous agencies that can charge or retain user fees for reinvestment into sustainable capacity strengthening to deliver core regulatory functions; others which are autonomous agencies may operate with inefficiencies and be unable to generate the funds or capabilities needed to strengthen their systems. Support to strengthen the capacity of NRAs has received increased attention in recent years but current funding levels are insufficient to meet the needs identified through application of the World Health Organization's Global Benchmarking Tool in the development of NRA Institutional Development Plans. Recent investments by the European Commission and the Bill & Melinda Gates Foundation and by some European governments are expected to go some way towards addressing this for regional anchor countries that are anticipated to become net producers of medical products.

- **The infrastructure needed to support an effective national regulatory system** – including the workforce, digital systems to facilitate effective information flows, an appropriate legal system – needs to be complemented by an infrastructure able to support networking across multiple agencies within a region, to facilitate efficiencies.

Other key challenges and investment opportunities across the regulatory lifecycle have been identified are as follows:

Facilitating R&D of vaccines

- Delay in clinical trial (CT) approvals, preventing rapid approval of CTs, which ultimately limits data generation and product-specificity for African populations

- Limited digital capacity (e.g., automated processes or mobile applications) to support oversight of complex CTs in Africa, making it a less attractive option for manufacturers to conduct trials in Africa
- Nascent coordination of activities between regulatory and ethics committees, creating bottlenecks to efficient CT approval. No clear model exists for the conduct of ethics reviews and approval roles; leads to fragmented and divergent approaches across the continent. Only for the first time during the COVID-19 pandemic, AVAREF was able to organize a meeting with regulators and ethics committees to grant approval at the same time

Authorizing safe and effective vaccines

- Duplicative processes of WHO PQ activities by RECs and NRAs. Inexperience with vaccine related technologies and dossiers has prevented NRAs to support or participate in reliance mechanisms due to lack of current trust in the decisions made by others
- Varying requirements and legislative processes creative duplicative processes for manufacturers, leading to staggered registrations and long timelines for the evaluation and authorisation of vaccines and medicines (creating a disincentive to launch)
- Lack of laboratory capacity for lot release
- Lack of well-established procedures for reliance on emergency use processes by SRAs by African NRAs
- Limited digital capacity to streamline marketing authorisation processes
- Lack of defined processes to support post-approval changes / variations. Capacity gaps to review and approve post-approval product variations leading to vaccine stock-outs and shortages, and further disincentivizes manufacturers to launch

Manufacturing and quality assurance

- Nascent technical know-how for oversight of vaccines and complex biologics. Few accredited sites limit the local manufacturing environment
- Limited capabilities in Good Manufacturing Practices (GMP) inspections and laboratory infrastructure, including for lot release which prevents expansion of local manufacturing

- Insufficient legal powers and coordination between stakeholders to deter those engaged in support of sub-standard and falsified medicines, resulting in insecure supply chains and increasing vaccine hesitancy

Deploying vaccines within countries

- Limited resources to enforce oversight of cold chain equipment and administration devices within WHO PQ to support effective vaccine roll-out
- Insufficient GDP and Good Storage Practices undermine market control needed to protect the stability and efficacy of vaccines

Monitoring ongoing safety and effectiveness

- Inadequate market surveillance to identify efficacy and quality issues in countries with limited regulatory capacity and small markets
- Nascent digital infrastructure and resources for reporting and analysing adverse events information within a continental or national pharmacovigilance (PV) system
- Limited capacity for many NRAs to conduct national PV activities (within a multi-country 3S framework)
- Limited ability for many NRAs to respond to issues identified and share the information effectively, resulting in poor response rates to adverse event (AE) issues and rapid withdrawal of products from markets

Additional challenges that can impede the long-term sustainability and effectiveness of the regulatory system in Africa cut across all regulatory functions along a product's lifecycle and include more systemic issues relating to financing, individual human resourcing, institutional and operational capacity, digital resources, and the legal and policy environment. Good performance in these areas is central to driving forward regulatory systems and improving the effectiveness of continental regulatory oversight.

The solutions to address many of the challenges are often known and proven to work in other settings. The concepts of work-sharing, harmonisation, and reliance are globally accepted as being able to support NRAs to deliver more efficient and effective regulatory oversight and have received attention in the last decade as means to reduce backlogs and

delays and promote good practice. Investments are needed to provide additional support for NRAs and regional and continental coordinating bodies in areas such as human resource training in regulatory sciences and operational delivery, professional development and networking; digital infrastructure to support processing and sharing of confidential data and information and improve networking outputs within and across regions; laboratory strengthening to support lot release of vaccines; pharmacovigilance systems to improve product safety; the clinical trials approvals process, which is often hampered by complex or opaque ethics requirements across countries; and building the evidence base, including monitoring of key performance indicators, to support decision-making and process improvements.

The report identifies the major interventions needed to either *maintain, improve* or *accelerate* sustainable change within the system. Solutions grouped under *accelerate* are given priority in this report, given the potential for the most transformational impact, yet funders should also make investments into the foundational elements of *maintain*, which are essential for the regulatory ecosystem to *improve*, and into the key elements of *improve,* which are required for the regulatory ecosystem to *accelerate* its progress and performance.

Across all the core regulatory functions and underpinning infrastructural and operational areas, there is a gap between estimated funding needs and current investment levels, albeit that this gap will be reduced in selected areas by recent funding announcements. The highest income countries in Africa will necessarily be called upon by funding partners to finance an increasing share of spending on regulatory systems strengthening as part of a wider emphasis on health systems strengthening, drawing on a user-fee model to increase financial sustainability wherever feasible. As such, priorities for funders include:

a) **The next stage of strengthening should build on current initiatives** and move towards convergence and harmonisation of regulatory standards and policies to increase efficiencies, reduce duplication and improve access to medical products.

b) **There are persistent challenges that need to be addressed.** These include technical issues for vaccines, such as complex ethics approvals processes that slow down clinical trials approvals and nascent data systems for oversight of clinical trials; lack of laboratory capacity to support lot release and a corresponding reliance

framework to support sharing of scarce resources; a legislative framework to ensure regulatory policies, procedures and tools for approvals and emergency use authorisations can be taken up at national level; the tools to support follow up in the market place and monitor ongoing safety and effectiveness; and issues also affecting a wider range of medical products, such as a legal and policy environment able to fully support regulatory reliance; laboratory capacity for bioequivalence testing and GMP to support local manufacturing of small molecules and post-marketing surveillance; sustainable financing; and gaps in the regulatory workforce, institutional capacities, and digital resources.

c) **Supporting the operationalisation of the African Medicines Agency (AMA) is a critical step for achieving regulatory excellence**, especially for approvals of complex products, creation of continental level guidance, implementation of fit-for-purpose integrative information management systems and capacity strengthening. The vision of the AMA is to foster a collaborative regional approach, building on and complementing the African Medicines Regulatory Harmonisation (AMRH) initiative, which underpins the work of the AMA. Support for AMA and AMRH should be done in alignment with the PAVM Framework for Action to tackle challenges in regulatory capacity for vaccines research, development and manufacturing and the WHO Resolution WHA 74.6 Strengthening local production of medicines and other health technologies to improve access and other related policy frameworks

d) **Efforts should be directed to strengthening anchor countries and key functions** across regional economic communities (RECs), continuing to develop local centres of excellence in specific regulatory activities, including laboratory testing, and reliance between NRAs and on regional, continental or global procedures for different regulatory functions

e) **Sustained investment in the following additional areas is essential to enable the transformational and impactful change needed** in Africa's regulatory system:

   i. **The legal and policy framework**: review of the outstanding issues concerning legal and policy reform, including the legal basis and framework for reliance and issues affecting suppliers, such as post-approval changes

ii. **Dedicated strengthening of key bodies**, such as the AMRH, REC secretariats, AMA secretariat, and the continental Technical Committees to support work-sharing and reliance

iii. **Cross-cutting infrastructure issues:** laboratory infrastructure, digital infrastructure, information management systems and workforce strengthening and retention, through the AMRH continental Technical Committees and RCOREs

iv. **Meaningful, transparent performance measurement** and management

v. **A robust strategy to sustainably finance** the above activities

This is a critical moment in the evolution of the African regulatory ecosystem for vaccines and medical products. There is a confluence of factors bringing about AMA Treaty Ratification in almost record time, reflecting a high level of political momentum both within Africa and beyond. Global funding partners should stand ready at the earliest opportunity to provide support to enable the AMA to emerge as an effective and leading part of the 'tool-kit' for achieving an efficient, scientifically robust, transparent, accountable regulatory system in Africa that supports patient access to safe, effective and quality medical products and enables local manufacturing of such products to flourish.

This will require investment at all levels of the ecosystem. Specific focal areas will of course need to be determined by funders' own strategic priorities, funds available, timing of their investments, and the additional value that they can bring to ensure the necessary political, technical, and funding inputs are available. The authors hope that this report will help funders make informed choices about their investments into regulatory systems strengthening in Africa and pursue further dialogue with partners to implement actions in a timely way.

2. Background

2.1. Africa's regulatory environment and key stakeholders

The regulation of vaccines and other medical products primarily aims to advance individual and public health goals by ensuring that products meet acceptable international standards of safety, quality and efficacy. Regulators undertake a range of activities including to authorise and supervise manufacturers, importers and distributors who are listed in the application of a medicine to be marketed, towards ensuring the safety, quality and efficacy of medical products, as well as the integrity of the supply chains through delivering products to patients. A secondary aim is to lift standards, support the emergence of a pharmaceutical industry and stimulate biomedical innovation. When a regulatory system performs well, patients and health systems may benefit from rapid and sustained access to quality, safe and effective products. When it under-performs, product availability is often delayed and costs to health systems, individuals and society are increased by the effects of substandard or falsified products, or a lack of access to life-saving commodities. In many resource-limited settings, there have historically been long delays associated with filing, approval and launch of medical products relative to their introduction in high income countries. For example, it has been estimated that in low- and middle-income countries (LMICs the overall time to registration for new, innovative medicines and vaccines) is typically four to seven years after submission of a marketing authorization dossier, compared with one to two years, on average, in high income countries (HICs)[1]. Notwithstanding this, much has been accomplished in the last decade to improve the efficiency and robustness of regulatory systems in Africa.

Despite making strides forward in terms of capacity to conduct a range of regulatory activities over the past decade, poor availability of vaccines and medical products in Africa has been attributed, at least in part, to weak and fragmented medicines regulatory procedures, policies and systems, a nascent workforce within National Regulatory Authorities (NRAs), limited collaboration between these bodies and those working in other areas along the value chain and insufficient reliance on work conducted by other stringent or mature agencies. Globally, the World Health Organisation (WHO) has estimated that only 30% of NRAs have capacity to perform core regulatory functions[2], and to-date only four African National Regulatory Authorities (NRAs), Tanzania, Ghana, Egypt and Nigeria

perform as Maturity Level 3 agencies for pharmaceuticals. Only Egypt has achieved a Maturity Level 3 for vaccine regulation of locally produced vaccines.[3] The situation is made more challenging by the increasing complexity of products that are available, something that affects the entire global regulatory community.

In this context, several complementary national, regional and global initiatives have been introduced to strengthen capacity, support regional harmonisation of regulatory standards and policies, and increase work-sharing and regulatory reliance. Most famously, the WHO Prequalification (WHO PQ) programme assesses and prequalifies finished pharmaceutical products, vaccines, active pharmaceutical ingredients, in vitro diagnostics, and vector control products and oversees manufacturing standards for many of the multilateral programmes that procure and supply medical products to low-income countries in Africa. The European Medicines Agency (EMA) also offers several regulatory pathways and initiatives to support reliance and collaborative work, including most notably the EU Medicines 4 All or Article 58 procedure which is a reliance approach that enhances information sharing, reduces registration times, and prevents duplication of efforts. This is a collaborative effort designed to facilitate registration and access to important medicines of high public health value that are destined for non-EU countries. Swissmedic's procedure for scientific advice and Marketing Authorisation for Global Health Products (MAGHP) aims to encourage and enable NRAs to make grant marketing authorisations following a Swiss marketing authorisation by building trust in the process and capacity among participating NRAs while involving WHO. The World Health Organisation's WHO-NRA Collaborative Registration Procedure (CRP) provides another means to accelerate country authorisation and registration for WHO Prequalified products. Additionally, the African Medicines Regulatory Harmonisation initiative (AMRH) aims to support technical standards harmonisation and convergence efforts along with procedural optimisation. It promotes work-sharing and reliance on stringent reference agencies, where possible. This includes reliance on NRAs with Maturity Level 4 designation (also known as Stringent Regulatory Authorities or SRAs) and using the WHO's Emergency Use listing procedure in the case of emergencies (including pandemics), or other collaborative procedures for epidemics and routine immunisation programmes.

These efforts, and others, aim in general to increase efficiencies, assure scientific robustness, and enable better allocation of scarce regulatory

resources. During the time of conducting research and writing this report a major milestone was achieved for improving the regulatory ecosystem for Africa, which is the coming into force of the African Medicines Agency (AMA) on 5th November 2021. According to the Treaty for the Establishment of the AMA, it will be a continental body delivered under, but independent of, the auspices of the African Union that will aim to support the pathway to regulatory convergence across the regulatory life-cycle in order to promote individual and public health and support the emergence of the local African pharmaceutical and vaccine manufacturing industries, ensuring that their products (as well as imported products) meet international standards of safety, quality and efficacy and that adverse events can be reported and appropriately acted upon. Building on the work of the AMRH and working through and in support of a network of NRAs across Africa, AMA will aim to offer expert scientific advice to countries and regional programmes on complex regulatory matters and focus on assessment of marketing authorisation applications for complex products including biologics and vaccines; simplify regulatory procedures and support work-sharing and regulatory reliance coordinated by the Regional Economic Communities; and provide transparency across the continent on certain regulatory activities/decisions, including the status of active pharmaceutical ingredients (APIs) and product safety. It is acknowledged that initially the scope of the products covered by the AMA will constitute around 5% of the marketing applications most African NRAs receive each year.

Once operationalised, the AMA will be governed by Member States that have ratified the AMA Treaty, via the Conference of State Parties, and aligned to the global norms and standards established by WHO and the International Conference on Harmonisation (ICH) and in accordance with the Treaty of the African Medicines Agency. It is intended that AMA will build on the efforts of the RECs - under the auspices of the African Medicines Regulatory Harmonisation (AMRH) initiative - which conduct multi-country joint dossier assessments of certain groups of non-WHO Prequalified products to enable more efficient and more scientifically robust product marketing application assessments by NRAs at the national level and joint inspections of manufacturing plants to ensure Good Manufacturing Practice (GMP).

Currently, all major vaccines for public health are reviewed by the WHO PQ programme and predominantly procured for African countries through multilateral initiatives such as Gavi, UNICEF or COVAX. WHO PQ will rely

on WHO Listed Authorities (WLAs) and, as countries graduate from support by donor-funded initiatives or if the scope or performance of WHO PQ were to change, reliance on the WHO PQ system itself may, in the long term, be supplemented by reliance on WHO Listed Authorities (WLAs)[4], some of which may eventually be on the African continent. Products that are out of the scope of WHO PQ will also need to be regulated by other trusted bodies, whether at the regional, local or national levels. An effective reliance model will be essential to ensure all African countries can benefit from these. Additionally, countries that currently or are anticipated to host vaccine manufacturers will need to have NRAs with Maturity Level 3 (vaccine producing) designation i.e. with access to the necessary vaccine lot release infrastructure to oversee them and assure that the vaccines manufactured meet international quality standards. This will ensure these vaccines are eligible for international procurement and support them in export markets. NRAs will also need the capacity to oversee clinical trials including bridging studies.

A system of effective regulatory reliance requires multiple domains of the African regulatory ecosystem to work effectively and in tandem, including:

- **National Regulatory Authorities (NRAs) working as WHO Listed Authorities** (i.e., at minimum Maturity Level 3 overall, and operating consistently over time at level 4 for the functions for which the agency is designated as WLA) such that they are accredited as scientifically and procedurally robust agencies and can thereby “expand the recognised pool of regulatory agencies with full capacity and performance by specific functions” (*ibid.*) and engage effectively in work-sharing and reliance activities, becoming reference agencies who share information as needed as well as potentially avoiding duplication of work done by trusted authorities elsewhere, when that work is relevant to the product under consideration by another regulatory authority.

- **NRAs working at Maturity Levels 1, 2, or 3 that can apply reliance principles** to expedite product registration and clinical trials approvals as needed.

- **Regional Economic Communities (RECs)** and regional public health agencies working to coordinate joint assessments and inspections by NRAs under the auspices of the AMRH initiative, providing recommendations to NRAs on marketing

authorisation/product registration and GMP certification and working to avoid repetition of the same reviews.

- **Users, particularly companies with products that are not eligible for WHO Prequalification, seeking market authorisation/product registration, GMP approval or clinical trials authorisation in multiple countries:** transparent, efficient collaborative regulatory procedures are needed, which avoid duplication at the national level, offering clear benefits to users to ensure consistent or increasing uptake of reliance pathways and avoid delays in product availability. Moreover, users (applicants) also have an important role to play in facilitating reliance, notably by providing unambiguous documentation that the version of the product they are submitting to the reliant agency is the same version of the product submitted to the reference agency. (i.e., manufactured on the same line at the same site as the version the reference agency assessed, etc.) and advocating for validated assessment reports (appropriately redacted, if needed) to be shared to enable corroboration of information.

- **Technical Committees of the AMRH and supporting technical partners** that conduct collaborative activities (such as AVAREF), and develop regulatory guidance, advice, and systems interventions applicable to all regulators across the continent. These work in alignment with recognised global norms and standards and in support of the African Union's public and economic health goals and objectives.

- **The African Medicines Agency:** A continental body in its infancy, aiming to address countries' technical or informational gaps by i) bringing together regulatory experts to conduct collaborative assessments and inspections for selected complex products that NRAs and RECs on the continent would, on their own, usually be unable to review; ii) developing guidance to support convergence of regulatory procedures and standards; iii) sharing relevant regulatory information that is essential for the efficient procurement and supply of international quality medical products and iii) communicating outputs at the pan-continental

level to increase the efficiency and effectiveness of the regulatory system.

- **System-oriented policies:** additional policies may be needed to address gaps in the system or coordinate elements to work together both within a country and across multiple countries to allow for national agencies to formally recognize or effectively rely on the work undertaken by trusted regulatory agencies. These may be legal – for example, the AU Model Law on Medical Products Regulation (AU Model Law) - or voluntary approaches that provide recommendations and influence action through information and communication. Digital tools to support rapid information sharing, collaboration, and reliance fall within this category.

- **Finance and related policies and financial partners/programmes** that ensure that regulatory functions and supporting systems interventions enable a regulatory model to work effectively and incentivise appropriate regulatory behaviour and action on the part of manufacturers and regulators.

- **Human resource policies and professional competency and performance frameworks** that provide clear recognition for work delivered through reliance and offer incentives to develop skills, know-how and the leadership needed to make a network-based model effective.

- **Operational policies** that make the processes attractive to industry

- **Political support and legislation** to underpin voluntary and mandatory incentives to participate in the work and effectively fulfil all regulatory functions to best effect

2.2. Investment opportunities

Any investment in Africa's regulatory ecosystem should support the African Union and its Development Agency, AUDA-NEPAD, to work with Regional Economic Communities (RECs), Member States' NRAs, the AMA governing bodies, the Partnerships for African Vaccine Manufacturing

(PAVM) and other stakeholders to improve outcomes in a range of global health domains to:

- Meet Sustainable Development Goal 3.8 (concerning health and well-being for all),
- Deliver the wider policy objectives of the African Union's (AU) 2063 Agenda,
- Facilitate implementation of the AU's Science, Technology, and Innovation Strategy for Africa 2024 (STISA) and the Pharmaceutical Manufacturing Plan for Africa (PMPA) (2005)
- Domesticate the AU Model Law on Medical Products Regulation (adopted by the AU Assembly in January 2016) to ensure effective regulation and promotion of harmonisation alongside capacity strengthening to develop core regulatory functions
- Operationalise the African Medicines Agency, based on the Treaty for its establishment, and thereby
- Maximise the opportunities offered by the African Continental Free Trade Area (AfCFTA) to build a single continental market for medical products that offers the advantages of scale and scope for businesses and to patients alike.

This is a unique moment in the political economy of medical products innovation and supply in which we are observing a confluence of political and scientific forces mobilising an array of tools to improve global health security. The establishment of the AMA reflects a high level of political commitment to the African Continental Free Trade Area, the strengthening of an African manufacturing base for a move towards local supply of vaccines and other medical products, and a regulatory ecosystem that helps assure that medical products from anywhere in the world are available to Africans and meet international quality, safety and efficacy standards and are not substandard or falsified. Additionally, COVID-19 has brought to the fore the need for more reliable and timely supply of essential medical products on the continent, which has prompted a resurgence of political support for local manufacturing and supply by African companies. This in turn has raised awareness of the need for commensurate regulatory oversight: for an effective and sustainable quality local manufacturing base to emerge in any country, the NRA needs to be operating at Maturity Level 3, able to conduct lot release for vaccines

and other biological products using WHO certified laboratories (either domestic or regional/global reference laboratories).

This offers an opportunity for those with an interest in Africa's public health and prosperity to reflect on how well the regulatory 'ecosystem' is working to support innovation and diffusion of essential medical products to patients across the continent. Now is the time to consider opportunities for further strengthening and accelerating improvements to this system and its various subsystems, particularly in relation to complex novel biological products such as vaccines.

Collective investment from global partners is needed to facilitate a functioning and sustainable regulatory ecosystem in Africa that meets international standards. Although several highly successful efforts currently exist to ensure that safe and effective vaccines and other medical products are available when and where they are needed, and others exist to strengthen harmonised regulatory practices to promote global convergence and the efficiencies that accompany it, it is evident that gaps remain. More can be done to strengthen the regulatory ecosystem, including reliance as an important element of the system that spans across core regulatory functions to improve access to safe and effective medical products.

Given this, the Wellcome Trust commissioned Charles River Associates ("CRA") and Harris Access Consulting Ltd. ("HAC") to provide recommendations to The Wellcome Trust, hereinafter referred to as Wellcome, for future areas of funding priorities that will further improve the performance and sustainability of the vaccine's innovation ecosystem in Africa, as well as offer benefits for the regulation of a wider set of medical products essential for the promotion of individual and public health.

3. Approach

To provide recommendations for investment, we followed three key steps as follows:

1. First, we conducted a thorough literature review to assess the existing national, regional, and continental approaches aimed at regulatory strengthening for vaccines in LMICs. To structure the research, we followed a framework that considered: aims of the initiative; activities conducted across the regulatory lifecycle; the extent they support regulatory sustainability, including capacity building, information sharing, harmonisation and reliance efforts; evidence of impact to-date; and barriers to progress and implementation. The review drew from a range of public sources including the academic literature, government/public health agencies, NGOs and consultancy reports. To complement the literature review we interviewed 20 global, regional, national and industry stakeholders to validate our understanding and gain their perspectives on the key challenges and potential solutions required to improve sustainability of the vaccines ecosystem (see Appendix 1: Table 2 for stakeholder list) and drew on our own experience of working on the African regulatory harmonisation agenda in the last decade.

2. Second, once the current regulatory challenges were categorised, we identified and prioritised opportunities for further regulatory strengthening. We followed a theory-of-change model to understand what potential inputs and regulatory activities are required to improve the performance and sustainability of the vaccine innovation ecosystem in Africa. When considering opportunities, we followed guiding principles when investing in regulatory strengthening which were developed in discussion with Wellcome. Solutions for consideration were then grouped based on the principle that the WHO's Global Benchmarking Tool indicators are the benchmark against which regulatory strengthening efforts should be focused and their impact assessed. These fall under three objectives, namely maintaining, improving and accelerating regulatory excellence.

3. Finally, we developed a set of prioritised recommendations on opportunities for investment across the regulatory lifecycle and in

cross-cutting and infrastructural areas. These aim to ensure identified challenges are addressed and systems are appropriately strengthened for all countries (those importing and those either manufacturing or aspiring to manufacture vaccines and other medical products), using reliance, coordination, harmonisation, recognition and work-sharing as the key principles for achieving these goals.

A list of abbreviations used in this report is included in the Appendix: Table 1.

4. Current regulatory landscape and challenges

4.1. Overview of existing regulatory reliance initiatives

There are several initiatives in place to facilitate product registrations of both medicines and vaccines in low- and middle-income countries (LMICs) to increase the rate and quantity of approvals of safe and effective international quality products (examples of such initiatives are illustrated in Figure 2). This includes the WHO's Pre-Qualification (WHO PQ) Programme, which publicly lists finished pharmaceutical products (FPPs) and active pharmaceutical ingredients (APIs), vaccines and immunisation devices, in vitro diagnostics, and vector control products that have been assessed and deemed to have met stringent standards of quality, safety and efficacy; ensures quality control of laboratories; provides training and advice to NRAs; and monitors ongoing quality of pre-qualified products.[5] The WHO-NRA Collaborative Registration Process (CRP) provides the central mechanism for ensuring a PQ-listed product can be translated efficiently into a national authorisation. The scope of the WHO PQ programme is currently limited to around 10% global health products on the WHO Essential Medicines List (EML) (i.e., those that are currently procured by UN and other international procurement agencies), meaning that around 90% of pharmaceutical products on the EML do not experience the expedited selection, procurement and supply pathways experienced by those on the PQ List (through, for example, the Global Fund for AIDS, TB and Malaria, Unicef and UNITAID as well as several NGOs conducting procurement and supply). For vaccines, however, most essential vaccines do go through the WHO PQ assessment process or through current Stringent Regulatory Authority processes prior to registration in LMICs. Opinion surveys report that there are still delays in access to certain subsets of vaccines in LMICs due to inconsistent requirements across NRAs and requirements to provide supplementary documentation and additional inspections beyond those required by WHO PQ.[6]

In this context, several complementary initiatives have been introduced to build capacity or support regional harmonisation of NRA standards and procedures to increase efficiencies, improve reliance on reference authorities, enable better allocation of resources and promote faster availability of quality-assured products. For the WHO PQ listed products, the WHO-NRA CRP is the leading approach to drive up the speed and

coverage of reliance on PQ by national authorities. In Africa, for non-PQ products, the most notable approach includes the African Regulatory Harmonisation initiative (AMRH) mentioned above, and complementary capacity strengthening efforts with NRAs aiming to reach Maturity Level 3 and Maturity Level 3 (vaccine producing).

As part of this study of the regulatory landscape for vaccines and other medical products in Africa, a literature review of key international initiatives globally was undertaken to understand their regulatory focus areas, evidence of impact and barriers to success (see Table 1) and assist with drawing insights for strengthening Africa's regulatory system.

Table 1: International initiatives investigated within the study

Primary focus for deep dive analysis

African Medicines Regulatory Harmonisation Initiative (AMRH)

- A harmonisation initiative based on a regional model of joint assessments and inspections, supported by continental technical committees that develop supplementary guidance and tools to aid convergence and improve regulatory processes

African Vaccine Regulatory Forum (AVAREF)

- A regional regulatory network founded by the WHO aimed at building regulatory capacity and promoting harmonization of practices focused mainly on multinational clinical trials authorisations (by regulators and ethics committees) (and now has been absorbed as one of the technical committees within the AMRH). Originally only focused on vaccines, it now focuses also on medicines and other medical products.

Pan American Health Organisation Strategic Fund (PAHO SF)

- A regional technical cooperation mechanism for pooled procurement of essential medicines and vaccines

Pan American Network for Drug Regulatory Harmonisation (PANDRH)

- An initiative of the national regulatory authorities within the region and the Pan American Health Organisation (PAHO) that supports the process of pharmaceutical regulatory harmonisation in the Americas, within the framework for nation and sub-regional health policies and recognising pre-existing asymmetries

The South East Asia Regulatory Network (SEARN)

- A regional initiative launched to enhance information sharing, collaboration and convergence of regulatory practices across the region

WHO Prequalification (PQ)

- A programme which publicly lists finished pharmaceutical products (FPPs), active pharmaceutical ingredients (APIs), vaccines, immunisation devices, in vitro diagnostics, and vector control products that have been assessed and deemed to have met international standards of quality, safety and efficacy, ensures quality control of laboratories, provides training and advice to NRAs and monitors on-going quality of pre-qualified products. In conjunction with WHO PQ, the WHO runs the WHO-NRA Collaborative Registration Process (CRP), which is a formal programme though which countries rely on WHO PQ listings when authorising products for marketing. Currently the central mechanism enabling countries to access donor-funded products, however the scope of medicines is limited to the 10% of products on the WHO Essential Medicines List (EML) purchased by UN and other procurement agencies. Most vaccines either go through WHO PQ or an SRA assessment before authorisation in LMICs

Secondary focus (gather high-level learnings)

The Caribbean Regulatory System (CRS)

- A regional initiative to support members of the Caribbean economic area (CARICOM) and the Caribbean Public Health Agency (CARPHA) to register medicines and conduct pharmacovigilance through a process primarily of verification that the versions of products being received in the countries are indeed the versions assessed by PQ and/or reference agencies.

The African Medicines Agency (AMA)

- A new pan-continental agency aiming to support and coordinate a network of continental regulatory authorities and Regional Economic Community Medicines Regulatory Harmonisation programmes. It will provide regulatory advice to NRAs (including marketing application assessment opinions for certain classes of products), issue guidance, coordinate some regulatory activities and procedures, enable discussion on policies affecting the continent, enhance regulatory harmonisation and support access to relevant information

and tools that support reliance, work sharing and regulatory convergence

The African Regulatory Network (ARN)

- Works in partnership with regulatory authorities to encourage greater harmonisation and convergence of regulatory requirements

Africa Regulatory Taskforce (ART)

- A temporary joint effort established by the Africa Centres for Disease Control and Prevention (Africa CDC), the African Union Development Agency (AUDA-NEPAD) to focus on COVID-19 vaccines in 2020-2021, in part superseded by the regulatory pillar of the Partnerships for African Vaccines Manufacturing (PAVM) that was established in April 2021 and its Framework for Action, which includes a regulatory pillar

The European & Developing Countries Clinical Trials Partnership (EDCTP)

- A programme of the European Union aiming to support biomedical innovation for neglected populations in Africa by supporting clinical trials and related functions, currently in its third programme

To map the existing regulatory strengthening landscape, each initiative was analysed in turn using a standardised framework; namely, aims, key activities throughout the regulatory lifecycle, focus on sustainability and evidence of impact. From the research, we identified the critical enablers for success, limitations of the initiative and potential solutions to support their impact. For each initiative, its area of focus in the regulatory lifecycle and the initiative's perceived impact was mapped (see Figure 1).

From this mapping exercise, we identified clusters of activities around clinical trials approvals and marketing authorisations/product registration but, outside of PAHO and to some extent WHO PQ, much less support for strengthening and harmonising ethics reviews for clinical trials; handling of post-approval changes; manufacturing, distribution and deployment; as well as post-marketing surveillance and pharmaco-vigilance. Some of these areas are altogether neglected by regulatory strengthening initiatives, some do not have impact data available, and others have not yet demonstrated impact, sometimes due to projects being relatively new (e.g., the African Union's Smart Safety Surveillance (3S) initiative on pharmacovigilance).

Figure 1: Areas of focus of selected international initiatives across the regulatory lifecycle

Initiative	Facilitating research and development of vaccines				Authorizing safe vaccines			Manufacturing and quality			Deploying vaccines		Monitoring ongoing safety and effectiveness	
	Scientific advice	Clinical trials	GCP guidelines	Ethics review	MA guidelines	MA joint reviews	Post approval changes	Quality / GMP	Batch inspection	GDP guidelines	Delivery	Procure ment	PV	Clinical guidelines
AVAREF	◕	●	●	◕	●	●	○	○	○	○	○	○	○	○
AMRH*	○	○	○	◕	●	●	○	◕	○	◕	○	○	◕	○
ARN	○	◔	○	○	◔	○	○	◔	○	○	○	○	◔	○
ART	○	○	○	○	●	●	○	○	○	○	○	○	○	○
EDCTP	○	◕	○	◔	○	○	○	○	○	○	○	○	○	○
CRS	◕	○	○	○	◔	●	◔	◕	○	○	○	○	◕	○
SEARN	○	○	○	○	◔	○	◔	◔	○	◔	○	○	◔	○
PQ**	○	○	○	○	●	●	●	●	○	○	○	◕	●	○
PAHO	●	○	●	●	●	●	●	●	○	○	○	●	●	●

Africa — LMIC — RoW

Key: ○ Not areas of focus; ◔ Area of focus – Low impact and uptake; ◕ Area of focus – Moderate impact and uptake; ● Area of focus – High impact and uptake

Source: CRA and HAC analysis

Abbreviations: GCP = good clinical practice, MA = marketing authorisation, GMP = good manufacturer practice, GDP = good distribution practice, PV = pharmacovigilance, LMIC = Low- and Middle-Income Countries, RoW = Rest of the World

Notes: Low, moderate and high determined by level of ***impact and uptake*** of efforts by the initiatives in a given area of the regulatory lifecycle, based on the literature and stakeholder feedback; MA joint reviews also include pooling recommendations at a regional level. Scientific advice can also include provision of scientific and technical information related to regulatory decisions

Current progress under the AMRH

AMRH is funded by private not-for-profit organisations and governmental agencies, on a *bilateral* basis direct to NRAs and coordinating bodies, including the RECs and AUDA-NEPAD; and through *multilateral* channels such as WHO, which in turn provides both funding (e.g., to the AUC for the operationalisation of the AMA) and technical assistance to both NRAs and regional initiatives.

Prominent AMRH funding partner organisations currently include The Bill & Melinda Gates Foundation (via a range of channels, including to AUDA-NEPAD, WHO, the RECs, direct to selected NRAs, and historically through the World Bank Trust Fund) and the Swiss Development Corporation (via direct funding to WHO). In 2021, funding was confirmed for AMRH from Germany's GIZ (via direct funding to AUDA-NEPAD). In February 2022, significant funding (100 million Euros or $113.93 million) was announced in a joint package from the European Union and Bill & Melinda Gates Foundation to support this initiative and the development of the African Medicines Agency, including for the European Medicines Agency to provide technical assistance to NRAs to reach Maturity Level 3 (via scientific collaboration, joint inspections, training)[vii]. Historically (2012-2021), the World Bank Global Medicines Regulatory Harmonisation Multi-Donor Trust Fund, now winding down, has provided a central mechanism for coordinated funding to support technical and project management inputs for the regional harmonisation initiatives, which included funds from the UK's Department for International Development (DFID) (2013-2020),

Gavi the vaccines alliance, The Bill & Melinda Gates Foundation and USAID.

From a technical perspective, the European and Developing Countries Clinical Trials Partnership (EDCTP), a programme of the European Union, also funded some of the early technical work of AVAREF. The United Nations Development Program (UNDP) provided early technical inputs, including for the development of the AU Model Law, which promotes the development of autonomous NRAs that strengthen their capacity to deliver five core regulatory functions and use regulatory reliance where appropriate. Additionally, a range of core technical partners have provided ongoing technical and strategic support for technical work, particularly through the AMRH Technical Committees. These include United States Pharmacopeia (USP), with the support of USAID, who have driven forward the agenda of the African Medicines Quality Forum (AMQF) and are now heavily involved in the African Medical Devices Forum (AMDF), both Technical Committees of the AMRH. The United States Food and Drug Administration (US FDA) also provided support for the establishment and development of the African Blood Regulators Forum (ABRF), a Technical Committee of the AMRH, which now receives support from several agencies including France's Etablissement de Sang Francais (ESF) and Germany's Physikalisch-Technische Bundesanstalt (PTB), the national metrology institute.

NRAs from Switzerland, Germany, Denmark, the United Kingdom and elsewhere have provided technical support that is coordinated by the WHO. This work supports African NRAs to strengthen their capacity (in alignment with the WHO Global Benchmarking Tool) and supports the AMRH Technical Committees to develop guidance and other tools to support regulatory harmonisation, when required. This has included support for AVAREF, AUDA, and the Africa CDC with development of the Africa Regulatory Taskforce's framework concerning facilitated market authorisations of COVID-19 vaccines.

AMRH advocacy partners include PATH, which has delivered workshops to bring together a range of stakeholders to promote uptake and domestication of the AU Model Law and raise awareness of the AMA and possible benefits of Treaty ratification. The full list of technical, advocacy and funding partners to the AMRH and the AMA is provided within Appendix 1: Table 4.

Notwithstanding the progress made towards regulatory change from AMRH and complementary efforts by partners, there is general agreement that the current regulatory ecosystem in Africa is yet fully not fit-for-purpose. For example, many sub-standard and falsified products still circulate on the continent; product registration at the national level of many products is still very low , slow and with heterogeneous requirements relative to the rest of the world; the number of clinical trials launched in Africa is low relative to the rest of the world (although this is not solely the fault of the regulatory system); there is very limited laboratory capacity for lot release (with the exception of South Africa); and products needed to address new epidemics historically have lacked a suitable pathway to expedite emergency use, although the facilitated pathway for COVID-vaccine resulted in the very efficient authorisation of the WHO EULed COVID vaccines.

The Regional Economic Communities (RECs) which underpin the regional joint assessment and inspection procedures of the AMRH have developed organically, with differing governance and investment levels and at varying rates of progress. In the East African Community (EAC), national uptake of regional recommendations has been relatively quick and nearly all of those products that have received a positive regional joint assessment have been filed by companies at the national level. Many positive effects are experienced by the NRAs participating in the REC harmonisation efforts, not least an increase in trust, information sharing, and technical capacities.

Uptake of use of the REC procedures by NRAs is voluntary, however. Consequently, in other RECs, national uptake can be relatively low. There are many reasons for this, including the lack of legal binding framework for NRAs to use REC recommendations for abridged reviews that are subject to time limitations (e.g. 30 days) and the resulting inconsistent use of abridged review procedures by NRAs, based on REC recommendations; duplication by some RECs of work already conducted by other authorities; and duplication by NRAs of the work already conducted by the RECs, resulting in more work for companies and sometimes longer timeframes for authorisation and product registrations. Linkage between REC regulatory work and regional procurement programmes has also not yet been established, and REC recommendations are unrecognised by many national procurers in their product selection and assessment processes (unlike with WHO PQ products). Additionally, most products are not submitted by companies to all of the countries for authorisation after a

regional positive joint assessment. This has led to problems with the idea of an internal regional market and a feeling by some of the smaller states that they do not benefit in the end from these regional efforts, as the products do not come to their citizens in the end.

In sum, there have been notable **outputs** of the AMRH (e.g., product dossiers reviewed and generating decisions within much shorter timeframes; more regulatory capacity as defined by the WHO Global Benchmarking Tool indicators), and positive **outcomes** (e.g., more rapid national authorisations and registrations in the EAC, supporting improved availability of safe and effective medicines). However, the **impacts** of the regional procedures on patient access are not yet obvious to many observers and use of the REC procedures is not growing at a significant rate. There is strong commitment by the majority of African NRAs, whose participation remains consistent in the most active RECs (EAC, ECOWAS and SADC). In a process of ongoing maturation, as regulators participate in the joint assessments, they gain confidence in the REC procedures and their NRA often then begin to use it. Reliable and consistent tracking of progress is needed, building on the work of the Centre for Innovation in Regulatory Sciences (CIRS), the WHO Global Benchmarking Tool and the AMRH M&E Indicators framework to enable better identification of successes and areas for improvement.

Looking ahead

A goal of several African manufacturing initiatives is to stimulate local manufacturing in order that Africa can rely on local suppliers for 60% of its needs within the next two decades (~2040) [viii]. To do this, NRAs in producing countries will need to be able to provide effective oversight of product quality and safety at international standards. Equally, the African Union Commission has committed to reducing the circulation of sub-standard and falsified products and certificates on the continent and to the development of a continental agency “invested in promoting the regulation of medical products across the continent”[ix].

The vision for the future is therefore to establish a continental body, The African Medicines Agency, founded on the principles of scientific robustness, transparency, accountability, international standards, reliance (where appropriate) and convergence, which builds on the work of the AMRH. The Agency will, if established as intended, help to facilitate coordination of selected regulatory activities and further harmonisation and

cooperation across Member States, RECs and global reference authorities to support NRAs with oversight of medical products for routine and emergency use. The foci of the AMA will be limited initially, and the current treaty does not provide for any binding decisions by the AMA. National authorisations will remain the mainstay of product authorisations on the continent for the foreseeable future.

4.2. Regulatory system challenges

The potential benefits of coordinated regulatory activity, such as work-sharing and regulatory reliance (including speed, efficiency and improved ability to attract industry into smaller markets), are by now well-noted and are considered 21st century best regulatory practices, codified in the WHO's Good Reliance Practices guideline. They include reducing the time taken for regulatory approvals for NRAs and manufacturers alike, improving health outcomes by speeding up availability of quality vaccines and other medical products for patients. Regional joint assessment and inspection efforts can increase efficiencies by enabling NRAs to share their resources and divide up regulatory work to mutual benefit and strengthen overall regional and continental regulatory capacity. Joint assessments and inspections to support product registration also enable NRAs to benefit from the expertise of SRAs and the WHO Prequalification programme to facilitate more efficient registration.

As noted earlier, there have been many strides forward in Africa in recent years through, for example, the creation of the regional assessment- and clinical trials assessment-focused initiatives under the AMRH and AVAREF, respectively; the development of emergency use provisions to expedite or fast track approvals informed by the actions and work products of reference agencies and WHO PQ in emergency contexts; and the strengthening of the WHO Prequalification programme which is recognised by most African regulators and procurers alike.

However, recent analysis suggests that unique challenges exist. For example, in October 2021 Wellcome published a report on '*An effective vaccine ecosystem equipped to meet the challenges of future infectious disease threats*', which identified priority challenges faced by vaccines going through late-stage development.[x] These challenges included:

1. Few NRAs globally able to regulate the primary licensure of a novel vaccine efficiently and flexibly

2. Lack of harmonisation on requirements for quality, efficacy, labelling, packaging and safety of biologicals & diagnostics across NRAs
3. Innovative clinical approaches being under-used to support product development because of low (perceived) regulatory acceptability.

While there is close collaboration is some cases (e.g., those procedures wholly owned by heads of agencies like in the Southern African Development Community, SADC), there are continuing challenges with keeping to the agreed timelines (both by regulators and manufacturers), ensuring that recommended products get filled by manufacturers across countries, and then getting marketing authorisation application assessment within agreed timelines. All of this undermines the evolution of an effective continental network and its ability to prepare for or adapt to changes, especially when that continental entity (AMA) does not have the authority to issues binding decisions on the member states. Closer collaboration would enable the regulatory community to tap into the expertise that exists across the continent. Lack of adherence to agreed timing by both manufacturers and regulatory agencies for selected procedures also undermines the predictability of the system for users and participants and reduces NRAs' ability to plan and effectively allocate resources.

Regulation particularly in pandemic contexts faces ongoing challenges, namely in support of: (1) Clinical trials authorisations that include multiple or single sites in African countries; (2) Timely market authorisation and post-approval changes and (3) Agreement on the data and frameworks to be used to determine product 'sameness', which underpins consistent approaches to quality assurance.[xi]

Below we catalogue the key regulatory challenges across the regulatory lifecycle in Africa.

Facilitating R&D of vaccines and other medical products

- **Delay in clinical trial (CT) approvals**, preventing rapid approval of CTs, which deters trials from Africa and results in little or no contribution of African clinical data in marketing authorization applications.
- **Limited digital capacity** (e.g., automated processes or mobile applications) to support oversight of complex CTs in Africa, making

it a less attractive option for manufacturers to conduct trials in Africa.

- **Nascent coordination of activities between regulatory and ethics committees**, with inconsistent and sequential processes creating bottlenecks to efficient CT approval (a global as well as African issue), and widely divergent ethics processes across countries that lead to delays. No clear model exists for the conduct of ethics reviews and approval roles; leads to fragmented and divergent approaches across the continent. Only for the first time during the COVID-19 pandemic, AVAREF was able to organize a meeting with regulators and ethics committees to grant approval at the same time.

Authorising safe and effective vaccines and other medical products

- **Duplicative processes of WHO PQ activities by RECs and NRAs.** Inexperience with vaccine related technologies and dossiers has prevented NRAs to support or participate in reliance mechanisms due to lack of current trust in the decisions made by others
- **Varying requirements and legislative processes creative duplicative processes for manufacturers,** leading to staggered registrations and long timelines for the evaluation and authorisation of vaccines and medicines (creating a disincentive to launch).
- **Lack of laboratory capacity for lot release** for vaccine producing countries and batch testing of vaccines for safety and quality post approval as well as lack of laboratory capacity to perform bioequivalence studies for generic medicines).
- **Lack of defined processes to support post-approval changes and variations.** Capacity gaps to review and approve post-approval product variations leading to vaccine stock-outs and shortages, and further disincentivizes manufacturers to launch.

Manufacturing and quality assurance

- **Nascent technical know-how for oversight of vaccines and complex biologicals.** Few accredited sites limit the local manufacturing environment. This includes lack of WHO approved laboratory sights to support manufacturing oversite, lack of

infrastructure to support scale up manufacturing processes and insecure supply chains.

- **Limited capabilities in Good Manufacturing Practices (GMP) inspections and laboratory infrastructure,** including for lot release which prevents expansion of local manufacturing.
- **Insufficient legal powers and coordination between stakeholders** to deter those engaged in support of sub-standard and falsified medicines, resulting in insecure supply chains, and increasing vaccine hesitancy.

Deploying vaccines within countries

- **Limited resources to enforce oversight of cold chain equipment and administration devices within WHO PQ** to support effective vaccine roll-out. Cold chain equipment and administration devices program is a critical aspect in WHO PQ but does not have the scale necessary to support vaccine deployment.
- **Insufficient GDP and Good Storage Practices** undermine market control needed to protect the stability and efficacy of vaccines.

Monitoring ongoing safety and effectiveness

- **Inadequate market surveillance** to pick up efficacy and quality issues in countries with limited regulatory capacity and small markets**.**
- **Nascent digital infrastructure** and resources for reporting, analysing and responding to adverse events information within a continental or national pharmacovigilance (PV) system**.**
- **Limited capacity for many NRAs to conduct national PV activities** (within a multi-country AU 3S or similar framework), with only 72% of countries having quality control laboratories and 63% being engaged in market surveillance[xii]**.**
- **Limited ability for many NRAs to respond to PV issues identified and share the information effectively**

There are also fundamental challenges which can impede the long-term sustainability and effectiveness of the regulatory ecosystem in Africa. These cut across the specific regulatory functions across a product's lifecycle and include more systemic issues relating to financing, individual human resourcing, institutional capacity, digital resources, and the legal

and policy environment. Indeed, these operational challenges often supersede the technical and scientific challenges. These are all central in determining the maturity of regulatory systems and the effectiveness of continental regulatory oversight.

Cross-cutting challenges impacting regulatory sustainability in Africa

Financing

- **Lack of autonomy and conflicting financing models can dis-incentivise NRAs to harmonise or invest in capacity strengthening**, due to the lack of a defined distribution of funds when conducting certain processes.
- **Limited industry incentives to participate** when there is currently no clear impact on eventual access and uptake and certain collaborative processes are repeated by regional projects and national agencies, adding time and additional layers of effort for an applicant.
- **Limited industry incentive to engage smaller markets where return is less**. Industry de-prioritisation of African NRAs with respect to responsiveness to queries, often prolonging overall time to authorisations.
- **Partner coordination challenges and information gaps about resourcing needs** have the potential to result in duplicative or diluted efforts in the long run.
- **Countries with lower levels of regulatory maturity** are less attractive to external donor support despite greatest need, potentially preventing them from effectively participating in reliance activities.
- **Challenges with grant and funding management**, preventing financial sustainability and progression of both inter and intra-country initiatives and of National Regulatory Authorities (NRAs).

Individual human resourcing

- **Varied levels of technical skills and sometimes inexperienced NRA workforce** limiting optimal use of resources, technical coordination, and progress in harmonisation activities.

- **Inconsistent professional recognition and workforce capacity** with rapid staff turnover, preventing the development and retention of expertise within NRAs.

Institutional capacity

- **In general, NRA experience has been focused on the assessment, approval and registration of generic medicines (which comprise the vast majority of products on the markets in Africa)** rather than new chemical entities (NCEs) or complex biologics.
- **Lack of domestication of the AU Model Law and political prioritisation of regulatory activities**, rendering some NRAs as sub-units within Ministries of Health rather than autonomous agencies, hindering investment by NRAs into institutional capacity and regional reliance activities.
- **Performance monitoring and reporting publicly by NRAs and AMRH REC initiatives is inconsistent,** undermining ability to track and report progress, identify weak spots, and communicate impact and improve accountability.
- **Laboratory capacity is lacking,** preventing the regulatory community from providing adequate oversight to and support of local manufacturers.

Digital resources

- **Insufficient digital infrastructure to support effective convergence/ harmonisation** and timely, secure exchange of regulatory information between countries. When available, data is not always distributed between NRAs and other stakeholders, leading to information asymmetries and poor reliance practices

Legal and Policy environment

- **Absence of a clear global regulatory framework for market authorisations and post-approval changes in the case of pandemics**, including the need for submissions in multiple countries, and inconsistent alignment to WHO Good Regulatory Practices, which can lead to supply shortages.
- **Insufficient use of existing reliance pathways that exist globally** which holds back the development of a common

understanding of product ‘‘sameness’ and Good Manufacturing Practice, duplicating work and undermining efficiencies.

- **Inability to rely on opinions of reference authorities for epidemics specific to Africa**, leading to delays in authorisation for vaccines for Africa.
- **Inconsistent political willingness** to participate in work-sharing and reliance due to perceptions about risks to sovereignty, resulting in inconsistent uptake of regional recommendations and onerous demands on companies seeking market authorization in multiple countries for products already reviewed by trusted Maturity Level 4 reference agencies; particularly problematic if legal basis is lacking for uptake of AMA recommendations/opinions.
- **Lack of a binding legal framework to underpin the AMA or AMRH,** meaning that there is no obligation by NRAs to adopt recommendations of joint procedures into national processes and no obligation by suppliers to register products in countries that are part of a collaborative effort, all of which undermines uptake and damages the effectiveness of the REC collaborative procedures.
- **Insufficient policy and legal framework to support reliance for lot release** based on strengthened reference National Control Laboratories within a regional network-based reliance model.

5. Opportunities for regulatory strengthening

Several potential solutions were considered to address the current gaps in the regulatory environment based on the challenges identified through the literature and stakeholder engagements. Solutions have been considered using a strategic approach to build on what works well and could be strengthened to generate transformational impacts (i.e. in improvements in the availability of quality vaccines and other medical products) and ensuring an African-centric multistakeholder approach.

We have developed a framework of opportunities based on a number of key principles:

- All countries should have basic regulatory capacity at national level (defined as ML3 by WHO), in alignment with the AU Model Law for Medical Products Regulation
- Countries and RECs work in a global system: Convergence with global standards and processes; reliance (when appropriate) on credible (stringent) regulatory authorities. This reduces duplication of regulatory efforts, resources and time, while maintaining national sovereignty[xiii]
- Global and continental collaborative regulatory efforts to be supported by individual regulators with Maturity Level 3-4 designation: Development of network of African ML3 anchor countries; facilitate sustainable knowledge transfer between ML4, ML3 and others
- The multi-layered, interdependent system underpinned by trust and mutual understanding through long term steady engagement.

Opportunities for investment can be categorised according to the extent they *maintain, improve, or accelerate* the changes needed to further strengthen the regulatory environment.

Figure 2: Framework for opportunities for investment based on overarching objectives for development partners


1. Maintain
2. Improve
3. Accelerate
Ensure current work continues and plug financing gaps needed to address immediate needs
Focus on developing existing initiatives and expanding their scope
Move towards regulatory excellence at a continental level through optimised operationalisation of AMA
Support value-for-money investments within the next 6–12 months by supporting existing AMRH workplans and IDPs
Domesticate AU Model Law across AU
Continue developing AMRH technical committees, RCOREs and IMS/data collection systems, and user fee systems, enabling delivery of the goals under AMRH and WHO PQ
Support value-for-money investments in next 12-24 months by developing anchor ML3 states in each REC including for vaccines
Seek alignment and standardisation of diverse product registration processes
Remove any duplication and inefficiencies in the system, including by increasing reliance across NRAs, improving regional guidance and ongoing monitoring
Roll out coordinated Technical Committee workplans across all key areas to focus on broader infrastructure development, beyond individual institutions
Develop a policy research agenda
Develop a concrete roadmap for AMA (defining the scope and interactions with AMRH/RECs and NRAs) and expand the potential for creating a continental legal framework
Increase cross-REC reliance
Harmonize regulatory procedures and standardize to a continental approach
Implement findings of policy research agenda & demonstrate results
Short-term: 6-12 months
Medium-term: 12-24 months
Long-term: 24 months +

Activities under '*Maintain* aim, in the short-term (6-12 months), to build on what works well by providing ongoing funding and ensuring that value-adding projects can continue. Activities under *Improve* focus on developing the AMRH and NRAs further and expanding their scope where needed, looking at 12–24-month timeline. Activities under *Accelerate* are those that aim to make impactful systemic change on a longer-term basis (24 plus months).

We contend that this is a critical moment in the evolution of the African regulatory landscape for medical products, with a confluence of factors bringing about the AMA Treaty Ratification in almost record time, reflecting a high level of political momentum, and building on the successes of the past decade in the regulatory systems strengthening space. A key component of *Accelerate* is providing catalytic and long-term support for AMA while strengthening the AMRH, recognising the AMA as a body with the potential to support transformative, sustainable regulatory systems change if it is underpinned by strong regional and national procedures and capacities.

5.1. Maintain

Activities under 'Maintain' aim, in the short-term (6-12 months), to build on what works well by providing ongoing funding and ensuring that value-adding projects can continue. Interventions in this category were selected based on:

- *Relevance*: activities should be supportive of the core principle of promoting regulatory reliance to strengthen the regulatory and innovation ecosystems for vaccines and other medical products in Africa

- *Additionality:* activities should address identified gaps for work that builds on existing initiatives to strengthen systems and seek to bring additional resource to the field

- *Timeliness*: activities should be responsive to current opportunities and ensure that committed work is delivered on time

- *Feasibility* to implement within 6-12 months, based on approvals for work given by AMRH Joint Secretariat, RECs or Technical Committees and readiness of project concepts

- *Value for money* offered, based on approvals by AMRH Joint Secretariat, RECs or Technical Committees and partner feedback

Proposed activities under in *Maintain* aim to:

1. **Continue the work of the AMRH** via support to:

    a. **The RECs**, mitigating the impacts of the closure of one of the World Bank Trust Funds (including providing continuity following termination of consultancy support to the REC projects)

    b. **The AMQF Technical Committee** (via WHO) to strengthen the quality management systems of Member States by supporting at least one national quality control laboratory to attain international quality standards recognition (ISO 17025/WHO PQ)

    c. **The AMQF Technical Committee** (via REC such as IGAD) for the implementation of a risk-based regional post-marketing surveillance system for quality of product on the market by supporting a regional PMS study

    d. **The Regulatory-Information Management Systems (R-IMS) Technical Committee** (via AUDA-NEPAD) for the implementation of basic R-IMS for NRAs, based on pre-existing open-source R-IMS, Pharmadex. This is an essential precursor to extensive regional and continental medicine regulatory collaboration and information sharing. This early step would include the following primary modules: 1. Premise Licensing 2. Product Licensing 3. Import and Export 4. GMP, all supported by modules for: 1. Finance 2. Document Library 3. Report 4. User Administration.

    e. **The AMRH Partnership Platform, particularly coordination of funders,** to support resource allocation and strategic alignment

    f. **Ensure sufficient funding of AMRH joint secretariat and all components** (RCOREs, TCs, IDPs)
        i. **Regional Centres of Regulatory Excellence (RCORES)** have been designated as institutions or

partnerships of institutions with specific regulatory science expertise and training capabilities that they pass to other regulators with less expertise. The mission of the RCOREs is to provide academic and technical training in regulatory science applicable to different regulatory functions and enhance skills through hands-on training. In its original conception, academic centers were to offer academic trainings while working with NMRAs who were to offer practical expertise. The training institutions work in collaboration with the regulatory authority to support each other.

ii. An evaluation of the RCOREs from 2014-2019 conducted by USAID's MTaPS programme identified several challenges and areas of opportunity for strengthening the RCORES. Support should include consistent funding for core activities; development and implementation of a monitoring, evaluation and learning framework; communication and stakeholder engagement; exchange programme with WHO-listed authorities; expansion of RCORE network to wider set of institutions including in Francophone Africa, and project management to support implementation for some RCOREs (via AUDA-NEPAD and/or direct to the RCORE institutions)[xiv].

2. **Ensure domestication of the AU Model Law across AU Member States,** particularly those with lower maturity levels, to promote financial sustainability, capacity strengthening and reliance (via PATH). This will enable ongoing country ratification of the AMA Treaty, which will require membership of more mature regulators and the expertise and experience they bring.

3. **Ensure all anchor countries are supported in achieving ML3 status through their IDPs.** In addition to ensuring all ML1-2 countries can rely on competent reference authorities and have national registration lists. Advocating for the removal of individual country procedural steps following centralized/AVAREF review and approval can help streamline authorization and access.

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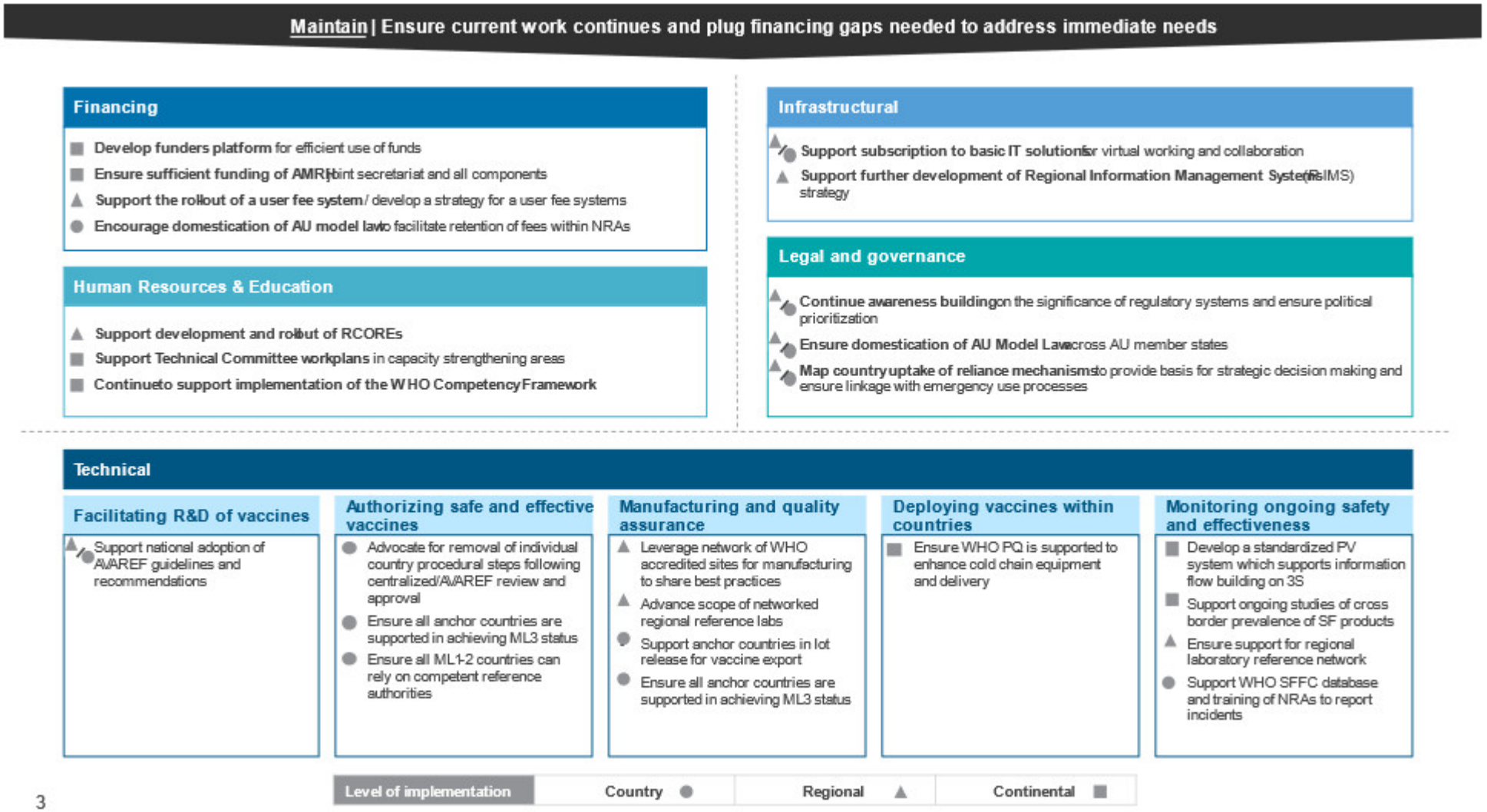
Maintain | Ensure current work continues and plug financing gaps needed to address immediate needs
Financing
Develop funders platform for efficient use of funds
Ensure sufficient funding of AMR Joint secretariat and all components
Support the rollout of a user fee system / develop a strategy for a user fee systems
Encourage domestication of AU model law to facilitate retention of fees within NRAs
Human Resources & Education
Support development and rollout of RCOREs
Support Technical Committee workplans in capacity strengthening areas
Continue to support implementation of the WHO Competency Framework
Infrastructural
Support subscription to basic IT solutions for virtual working and collaboration
Support further development of Regional Information Management System (RIMS) strategy
Legal and governance
Continue awareness building on the significance of regulatory systems and ensure political prioritization
Ensure domestication of AU Model Law across AU member states
Map country uptake of reliance mechanisms to provide basis for strategic decision making and ensure linkage with emergency use processes
Technical
Facilitating R&D of vaccines
Support national adoption of AVAREF guidelines and recommendations
Authorizing safe and effective vaccines
Advocate for removal of individual country procedural steps following centralized/AVAREF review and approval
Ensure all anchor countries are supported in achieving ML3 status
Ensure all ML1-2 countries can rely on competent reference authorities
Manufacturing and quality assurance
Leverage network of WHO accredited sites for manufacturing to share best practices
Advance scope of networked regional reference labs
Support anchor countries in lot release for vaccine export
Ensure all anchor countries are supported in achieving ML3 status
Deploying vaccines within countries
Ensure WHO PQ is supported to enhance cold chain equipment and delivery
Monitoring ongoing safety and effectiveness
Develop a standardized PV system which supports information flow building on 3S
Support ongoing studies of cross border prevalence of SF products
Ensure support for regional laboratory reference network
Support WHO SFFC database and training of NRAs to report incidents
Level of implementation
Country
Regional
Continental

3

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5.2. Improve

Activities under *Improve* focus on developing the AMRH and NRAs further and expanding their scope where needed, looking at 12–24-month timeline. Activities in this category would focus on:

1. **Support RECs and Technical Committees to streamline the regional collaborative assessment and clinical trial assessment approvals processes and the efficient use by NRAs of those assessments for national authorisations and develop solutions to improve the emergency use reliance pathways**. This would require a multifactorial and dynamic approach to target a range of challenges within REC MRH processes; in relation to NRA uptake of recommendations, improvements in national and regional procurement based on REC recommendations; and concerning manufacturer decisions to register and launch products in all relevant markets. A performance-based approach would be needed to monitor and communicate progress as an incentive for manufacturers and Member States to increase participation.

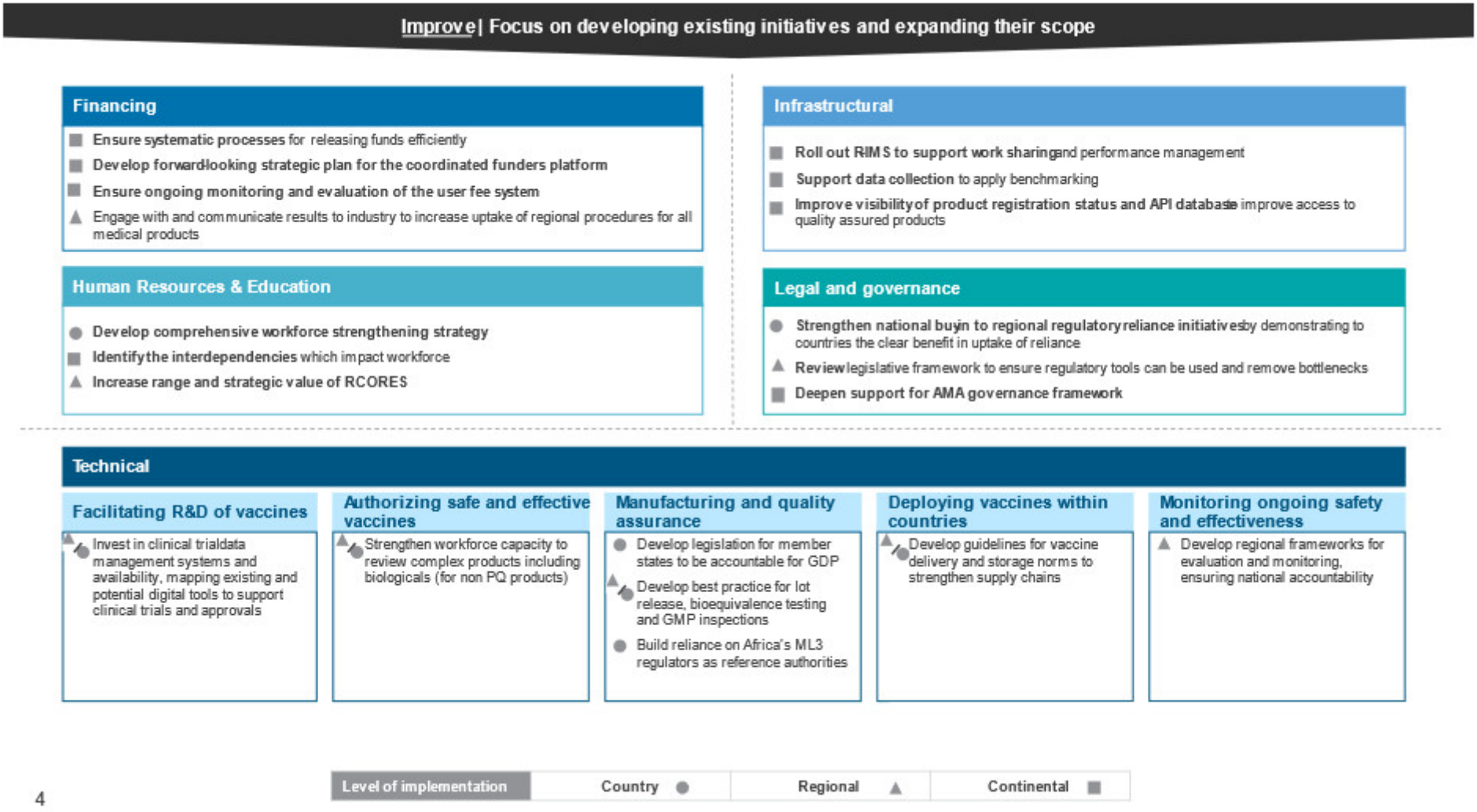
2. **Support NRAs to avoid duplication of WHO PQ reviews and those of other reference authorities and increase uptake of the AMRH REC recommendations and various other regulatory tools**. Again, this would require a multifactorial approach and draw on a range of levers across the regulatory system and in the wider health system.

3. **Ensure sustainable financing**. This requires several interventions, not least domestication of the AU Model Law and political will.

4. **Support development of the infrastructure for regulatory reliance, including the Regulatory-Information Management System (R-IMS).** The basic R-IMS approach for NRAs is seen as a prerequisite for the Regional R-IMS Solution and Information-Sharing Platform that would be used predominantly by the RECs. This would offer a system to make joint product evaluation and sharing confidential information more convenient, using an integrated R-IMS solution to provide real-time medicine regulatory information that is connected to the NRAs. This may require

implementation of complementary training of users across NRAs and RECs and development of materials/manuals.

5. **Develop comprehensive workforce strengthening strategy** with clear baseline and workforce targets for partners to create visibility on workforce needs, to include secondments between NRAs to support knowledge sharing. This could include identifying the interdependencies which impact workforce retention such as digital capacity, compensation, training, performance incentives, leading to increased range and strategic value of the RCORES.


Improve | Focus on developing existing initiatives and expanding their scope
Financing
Ensure systematic processes for releasing funds efficiently
Develop forward-looking strategic plan for the coordinated funders platform
Ensure ongoing monitoring and evaluation of the user fee system
Engage with and communicate results to industry to increase uptake of regional procedures for all medical products
Infrastructural
Roll out RIMS to support work sharing and performance management
Support data collection to apply benchmarking
Improve visibility of product registration status and API database to improve access to quality assured products
Human Resources & Education
Develop comprehensive workforce strengthening strategy
Identify the interdependencies which impact workforce
Increase range and strategic value of RCORES
Legal and governance
Strengthen national buy-in to regional regulatory reliance initiatives by demonstrating to countries the clear benefit in uptake of reliance
Review legislative framework to ensure regulatory tools can be used and remove bottlenecks
Deepen support for AMA governance framework
Technical
Facilitating R&D of vaccines
Invest in clinical trial data management systems and availability, mapping existing and potential digital tools to support clinical trials and approvals
Authorizing safe and effective vaccines
Strengthen workforce capacity to review complex products including biologicals (for non PQ products)
Manufacturing and quality assurance
Develop legislation for member states to be accountable for GDP
Develop best practice for lot release, bioequivalence testing and GMP inspections
Build reliance on Africa's ML3 regulators as reference authorities
Deploying vaccines within countries
Develop guidelines for vaccine delivery and storage norms to strengthen supply chains
Monitoring ongoing safety and effectiveness
Develop regional frameworks for evaluation and monitoring, ensuring national accountability
Level of implementation
Country
Regional
Continental

4

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5.3. Accelerate

Activities under *Accelerate* focus on developing transformational change to achieve regulatory excellence at a continental level, looking at a timeline up to 10 years. Activities in this category would focus on:

1. **Early engagement with AMA governing bodies and AMRH to support AMA operationalisation and integration into the wider regulatory ecosystem**, including:

    a. **Working with partners in development of a roadmap for AMA implementation and integration:**

        - Building on the 2019 *AMA Operational and Business Plan* to provide complementary support to the work of the NRAs and RECs in alignment with the AMRH REC and Technical Committee structures.

        - Using the 'anchor countries' to provide a firm technical and market basis (anchor countries designated informally, based on, size of the pharmaceutical market and regulatory maturity, as follows: **South Africa, Kenya, Nigeria, Ghana, Ethiopia and Tanzania) and those with significant vaccine manufacturing aspirations)** (via AMRH Partnership Platform).

        - Relying on other regulatory authorities (e.g., traditional SRAs and WHO PQ) as needed and as appropriate for technical opinions, guidelines development, data on products assessments and inspections, etc.

    b. **Addressing the legal and policy challenges faced by stakeholders,** based on technical analysis of a range of issues affecting the regulatory ecosystem, as set out in 3 a and b below, **providing multi-year funding in support of the digital infrastructure and human capital** and **strengthening the legal and policy environment**

2. **Supporting anchor country NRAs to attain Maturity Level 3 (vaccine producing)** such that they pass a WHO assessment of defined vaccine-related functions, including lot release (via bilateral

support, EMA and/or WHO, to complement the EC/ BMGF funding partnership).

3. **Providing large scale multi-year funding for regulatory system enablers** including:

    a. **Developing the digital infrastructure** (via AUDA-NEPAD/R-IMS): Development of regulatory information management systems for NRAs and RECs (known as R-IMS), and eventually the AMA and the linkages across these groupings (via AUDA-NEPAD and R-IMS Technical Committee Joint Action Group).
        1. Scoping feasibility of innovative IMS 'future ready' approaches including 'Accumulus Synergy' (an existing information sharing platform to support interaction of NRAs and RECs on a single platform), and blockchain
        2. Roll-out of R-IMS for NRAs (based on adaptation of system known as 'Zanzibar' and or integration with a platform such as 'Accumulus Synergy')
        3. Roll-out of R-IMS for RECs (based on adaptation of Pharmadex system and/or integration with a platform such as 'Accumulus Synergy')
        4. Centralised collection of performance data, aligned to the WHO Global Benchmarking Tool
        5. Centralised continental listing of current REC-recommended products and NRA authorisations linked to these
        6. Systems operable at the NRA level to facilitate workflow management, review coordination and documentation, financial management, and performance metric tracking and reporting.

    b. **Strengthening the legal and policy environment**. **The proposed programme could include** (to be supplemented by additional items provided in the concluding remarks and others that emerge in ongoing stakeholder discussions):
        1. **Scoping the potential for and feasibility of a revised legal framework to underpin the AMA** that mandates conversion of REC and AMA recommendations/opinions

into national registrations by NRAs and suppliers, providing a basis for procurers to expedite quality assurance reviews (via Joint Action Group for AMRH Medicines Policy and Regulatory Reform – MPRR - Technical Committee).

2. **Review and revision of REC procedures to improve efficiencies and uptake**, ensuring proper use of regulatory information by trusted sources and non-duplication of regulatory activities already conducted by trusted authorities.
3. **Refinement and streamlining of clinical trials and ethics processes** to promote concurrent rather than sequential decision-making (via AVAREF), with a focus on ethic board standards and procedures harmonisation.
4. **Institutionalise for other products the framework for emergency use authorisations by SRAs/reference authorities used in with the WHO EULed COVID vaccines.**
5. **Scoping the potential for AMA to adapt CHMP procedures for offering scientific opinions on marketing applications.**
6. **Connecting procurement processes with regional regulatory opinions to increase impact of harmonisation on product availability**, based on feasibility scoping study of a PAHO-type model for Africa (in discussion with other partners) for vaccines and other medical products.
7. **Developing regional quality assurance policies** to address the disconnect between regulatory and procurement policies (such that procurement policies recognise REC/AMA recommendations in support of abridged quality assurance reviews and give priority to those products even if they cost more).
8. **Scoping study on standardised approaches for harmonising ethics review standards and procedures including potential for inclusion of ethics review into AU Model Law**
9. **Review of post-approval changes (PAC) system:** scope the potential for an effective end-to-end process based on reliance, harmonising procedures across regulators for

timely PAC to be approved to support registration at national level and to prevent stockouts due to unauthorised PACs – especially of vaccines.

10. **Review of outstanding country concerns over AMA procedures and jurisdiction and options to address these.**
11. **Review of legislative framework and potential bottlenecks in support of reliance on join laboratory resources for lot release and bioequivalence**

c. **Providing technical and advocacy support to AMA, the AMRH Steering Committee, the AMRC and international forums** such as ICH, ICDRA and ICMRA to implement recommendations emanating from AMRH Joint Secretariat policy research programme (as per 3b above) (via AMRH Joint Secretariat and in collaboration with partners).

d. **Building institutional capacity and strengthening the regulatory workforce:**

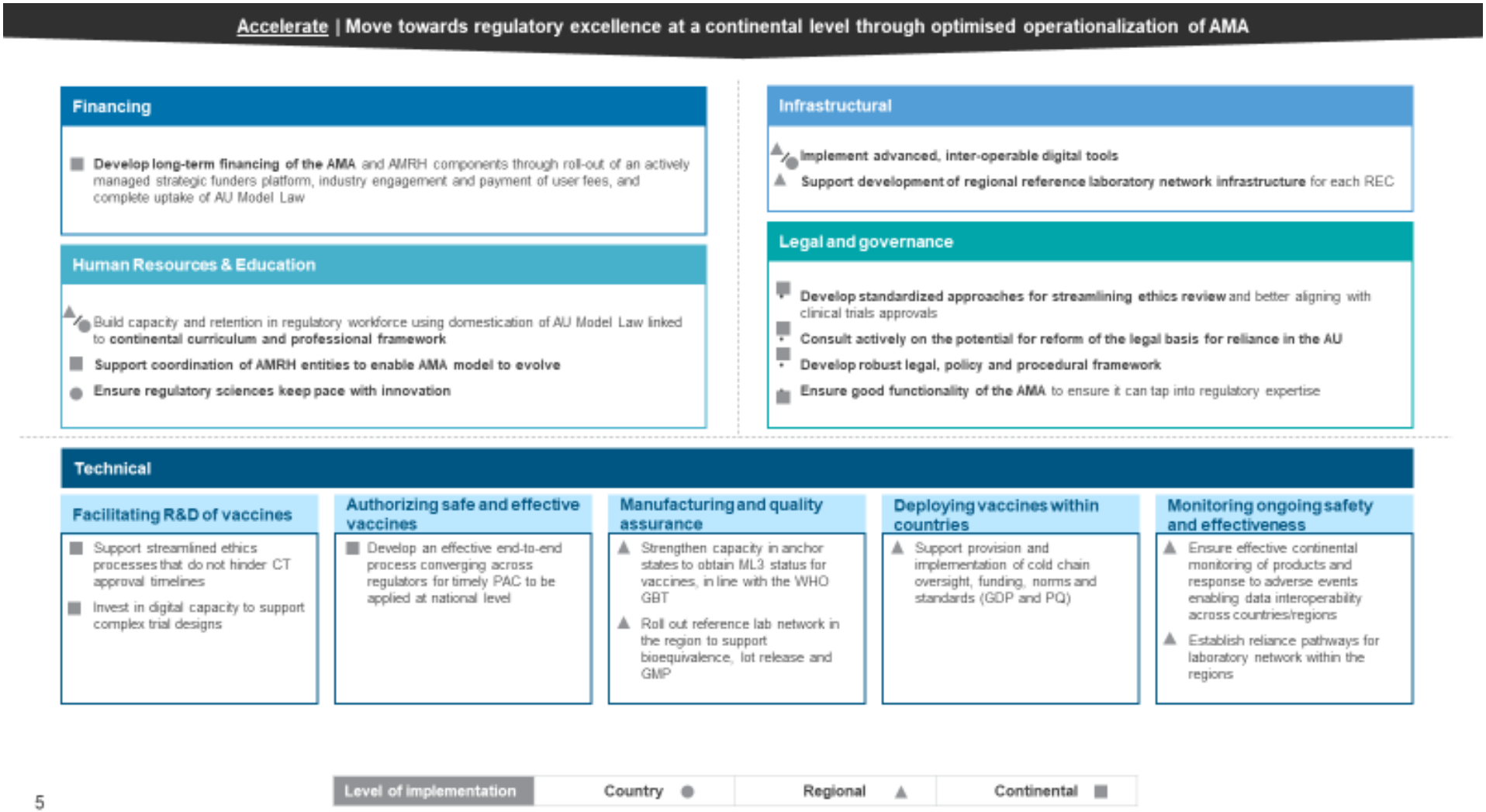
1. **Fellowships to provide professional training and work experience for regulators** (via WHO and NRAs in high-income countries, pursuing NRAs that are procedurally relevant to the African NRAs, except for the networking part of the AMA, including those in 'Access' – a consortium of regulators from Canada, Singapore, Switzerland and the United Kingdom – rather than, for example, US FDA or the EMA).

2. Additionally, the technical remit of the RCOREs should be reviewed and updated, providing specific support for regulatory oversight for vaccines and ensuring proper uptake of regulatory policies, procedures, and tools by countries. RCOREs may be able to take on aspects the evidence research programme outlined above.

e. **Strengthening network-based laboratory systems in support of local manufacturing and imported products, including capacity for joint lot release and bioequivalence**

by a reference National Control Laboratory (via WHO, building on AMRH African Medicines Quality Forum and related investments of Paul Ehrlich Institute, Germany, USP-Ghana Promoting Quality Medicines Plus (PQM+) USAID-funded programme and Coalition for Epidemic preparedness Innovations (CEPI)):

1. Creation of regional hub-and-spoke networks of national vaccine control laboratories involved in testing of non-prequalified products, based on strengthened capacity of selected reference laboratories (one per REC); appropriate harmonised continental framework for reliance; national reliance policies towards laboratory testing and lot release; and risk-based approaches
2. Increased participation by NRAs in global network of national vaccine control laboratories involved in testing of WHO-prequalified vaccines, based on
   - Strengthened capacity of selected National Control Laboratories to perform the evaluation of batches of WHO Prequalified vaccines before they are released onto the market (lot release) and
   - Development by NRAs of risk-based testing approaches with reliance on the outcomes of the lot release done by other regulators in the network.


Accelerate | Move towards regulatory excellence at a continental level through optimised operationalization of AMA
Financing
Develop long-term financing of the AMA and AMRH components through roll-out of an actively managed strategic funders platform, industry engagement and payment of user fees, and complete uptake of AU Model Law
Human Resources & Education
Build capacity and retention in regulatory workforce using domestication of AU Model Law linked to continental curriculum and professional framework
Support coordination of AMRH entities to enable AMA model to evolve
Ensure regulatory sciences keep pace with innovation
Infrastructural
Implement advanced, inter-operable digital tools
Support development of regional reference laboratory network infrastructure for each REC
Legal and governance
Develop standardized approaches for streamlining ethics review and better aligning with clinical trials approvals
Consult actively on the potential for reform of the legal basis for reliance in the AU
Develop robust legal, policy and procedural framework
Ensure good functionality of the AMA to ensure it can tap into regulatory expertise
Technical
Facilitating R&D of vaccines
Support streamlined ethics processes that do not hinder CT approval timelines
Invest in digital capacity to support complex trial designs
Authorizing safe and effective vaccines
Develop an effective end-to-end process converging across regulators for timely PAC to be applied at national level
Manufacturing and quality assurance
Strengthen capacity in anchor states to obtain ML3 status for vaccines, in line with the WHO GBT
Roll out reference lab network in the region to support bioequivalence, lot release and GMP
Deploying vaccines within countries
Support provision and implementation of cold chain oversight, funding, norms and standards (GDP and PQ)
Monitoring ongoing safety and effectiveness
Ensure effective continental monitoring of products and response to adverse events enabling data interoperability across countries/regions
Establish reliance pathways for laboratory network within the regions
Level of implementation
Country
Regional
Continental
5

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6. Concluding remarks

This research has identified the key challenges in the existing regulatory environment for vaccines in Africa, spanning across the regulatory lifecycle. The recommendations aim to ensure the continued work of the AMRH and its partners while also targeting areas with the potential for greatest transformational change, as follows:

a). The next stage of strengthening should build on current initiatives and move towards convergence and harmonisation of regulatory standards and policies to increase efficiencies, reduce duplication and improve access to medical products.

b). There are persistent challenges that need to be addressed. These include technical issues for vaccines, such as complex ethics approvals processes that slow down clinical trials approvals and nascent data systems for oversight of clinical trials; lack of laboratory capacity to support lot release and a corresponding reliance framework to support sharing of scarce resources; a legislative framework to ensure regulatory policies, procedures and tools for approvals and emergency use authorisations can be taken up at national level; the tools to support follow up in the market place and monitor ongoing safety and effectiveness; and issues also affecting a wider range of medical products, such as a legal and policy environment able to fully support regulatory reliance; laboratory capacity for bioequivalence testing and GMP to support local manufacturing of small molecules and post-marketing surveillance; sustainable financing; and gaps in the regulatory workforce, institutional capacities, and digital resources.

c). Supporting the operationalisation of the African Medicines Agency (AMA) is a critical step for achieving regulatory excellence, especially for approvals of complex products, creation of continental level guidance, implementation of fit-for-purpose integrative information management systems and capacity strengthening. The vision of the AMA is to foster a collaborative regional approach, building on and complementing the African Medicines Regulatory Harmonisation (AMRH) initiative, which underpins the work of the AMA. Support for AMA and AMRH should be done in alignment with the PAVM Framework for Action to tackle

challenges in regulatory capacity for vaccines research, development and manufacturing and the WHO Resolution WHA 74.6 Strengthening local production of medicines and other health technologies to improve access and other related policy frameworks

d). Efforts should be directed to strengthening anchor countries and key functions across regional economic communities (RECs), continuing to develop local centres of excellence in specific regulatory activities, including laboratory testing, and reliance between NRAs and on regional, continental or global procedures for different regulatory functions

e). Sustained investment in the following additional areas is essential to enable the transformational and impactful change needed in Africa's regulatory system:

i. The legal and policy framework: review of the outstanding issues concerning legal and policy reform, including the legal basis and framework for reliance and issues affecting suppliers, such as post-approval changes

ii. Dedicated strengthening of key bodies, such as the AMRH, REC secretariats, AMA secretariat, and the continental Technical Committees to support work-sharing and reliance

iii. Cross-cutting infrastructure issues: laboratory infrastructure, digital infrastructure, information management systems and workforce strengthening and retention, through the AMRH continental Technical Committees and RCOREs

iv. Meaningful, transparent performance measurement and management

v. A robust strategy to sustainably finance the above activities

Three key takeaways for investors:

1. **Support the operationalisation of the AMA** as a fundamental strategic pillar, including the AMRH which underpins the new agency
2. **Strengthen anchor countries** through collective efforts to achieve ML3 status and increase collaborative actions such as centralised joint laboratory services
3. **Provide combined support for the regulatory infrastructure**: including digitalisation of regulatory processes, investment in local

workforce retention and policy research and strategy support; strengthen basic infrastructure and foundation for local NRAs to build on

There is significant opportunity for those with an interest in Africa's public health and prosperity to consider opportunities for strengthening and accelerating regulatory system improvements. Moreover, with the AMA treaty gaining traction, including ratification by 22 African Union Member States (correct at time of publication), global investors should stand ready at the earliest opportunity to provide support to enable the AMA underpinned by the AMRH to emerge as an effective and leading part of the 'tool-kit' for achieving an efficient (including reliance-based where appropriate), scientifically robust, transparent, accountable regulatory system in Africa that supports patient access and enables local manufacturing of safe and effective medical products to flourish.

Appendix 1: Tables and Graphs

Table 1: Glossary of terms

Acronym	Definition
AE	Adverse event
AMA	African Medicines Agency
AVAREF	African Vaccines Regulatory Forum (although it also covers medicines)
AMRH	African Medicines Regulatory Harmonisation initiative
AU	African Union
AU 3S	African Union Smart Safety Surveillance initiative on pharma-covigilance
CTC	Clinical Trials Community
CTs	Clinical Trials
EDCTP	European & Developing Countries Clinical Trials
EMA	European Medicines Agency
EUA	Emergency Use Authorisation (various agencies)
EUL	Emergency Use Listing (WHO)
FDA	Food & Drug Administration (US)
GAVI	Gavi, The Vaccine Alliance
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
MoH	Ministry of Health
NAFDAC	National Agency for Food & Drug Administration (Nigeria's Na tional Regulatory Authority)
NECs	National Ethics Committees

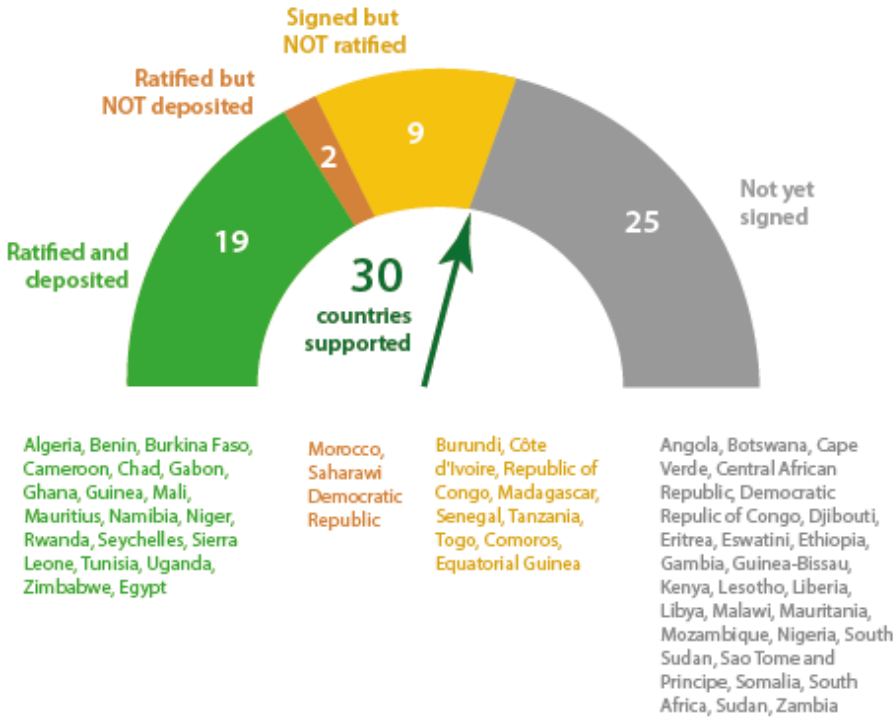
NRAs	National Regulatory Authorities
PAC	Post-approval changes
PQ	Pre-qualification
PV	Pharmacovigilance
RCOREs	Regional Centres of Regulatory Excellence
RECs	Regional Economic Communities
WHO	World Health Organization

Table 2: Stakeholders interviewed in the study

Stake-holder	Organiza-tion	Name	Role
Global	**WHO**	**Samvel Azatayan**	Team lead, RCN, REG, RPQ
Global	**BMGF**	**Murray Lumpkin**	Deputy Director Integrated Develop-ment / Global Regulatory System Initiatives Lead
Global	**BMGF**	**David Mukanga**	Senior Program Officer Regulatory Affairs
Global	**World Bank**	**Andreas Seiter**	Global Lead Private Sector in Health, Nutrition and Population
Global	**CEPI**	**Adam Hacker**	Head of Global Regulatory Affairs (UK and NA)
Global	**CEPI**	**Malika Al-mansouri**	Leading regional efforts in Africa and the Middle East
Global	**UNICEF**	**Shanelle Hall**	Ex-Deputy Executive Director
Global	**FDCO**	**Saul Walker**	COVID response lead

Global	**Gavi**	**Tiziana Scarnà**	Senior Manager, Innovation and Special Projects, Market Shaping
Regional	**AVAREF**	**Delese Mimi Darko**	Founding member of AVAVREF, CEO Ghana FDA
Regional	**AVAREF**	**Bartholomew Dicky Akanmori**	Regional Advisor, WHO AFRO
Regional	**CARPHA**	**Rian Marie Extavour**	Technical Coordinator at Caribbean Public Health Agency
Regional	**PAHO / PANDRH**	**Analia Porras**	Unit Chief, Medicines and Technologies, PAHO
Regional	**EDCTP**	**Michael Makanga**	Executive Director
Regional	**EDCTP**	**Thomas (Tom) Nyirenda**	Strategic Partnerships and Capacity Development Manager
Regional	**Africa Union / CDC**	**John Nkengasong**	Director (former), also African Union Commission
Regional	**EMA**	**Emer Cooke**	Executive Director
Regional	**SAPHRA**	**Helen Rees**	Board Chairwoman, Chief Regulatory Officer
National	**NAFDAC**	**Christianah Moji Adeyeye**	Director General
Industry	**Merck (MSD)**	**Ginny Acha and Angelika Joos**	Executive Director, Global regulatory policy
Industry	**IFPMA**	**Laetitia Bigger**	Director, Vaccines Policy

Figure 1: African Medicines Agency status of support as of 03/02/22



Source: African Union infographics.[XV] *States "supporting" refers to countries that have signed treaty and/or ratified the treaty. Two states, Burkina Faso and Namibia ratified and deposited the treaty without ever signing it formally.*

Table 3: List of technical, advocacy and funding partners to the AMRH and AMA

Technical Partners
Bill and Melinda Gates Foundation
European Medicines Agency
Danish Medicines Agency
European Directorate for the Quality of Medicines (EDQM)
Expertise France
USAID Medicines, Technologies, and Pharmaceutical Services (MTaPS) Program/Management Sciences for Health
United States Pharmacoepia (USP)/PQM+
Physikalisch Technische Bundesanstalt (PTB)
SwissMedic
Drugs for Neglected Diseases initiative (DNDi)
European Developing Countries Clinical Trials Partnership (EDCTP)
Family Health International (FHI360)
WHO Collaborating Centre for the Quality Assurance of Medicines (CENQAM)
International AIDS Vaccine Initiative (IAVI)
United Nations Population Fund (UNFPA), Procurement Services Branch, Copenhagen
BfArm -Federal Institute for Drugs and Medical Devices, Germany
Coalition for Epidemic Preparedness Innovations (CEPI)
University of Kwazulu-Natal (UKZN)

African Society for Laboratory Medicines (ASLM)
Africa Collaborative to Advance Diagnostics (AFCAD), Africa CDC
International Society for Blood Transfusion (ISBT)
CHMP (Humuanitarian Centre for Pharmacy Professions/Centre Humanitaire des Metiers de la Pharmaceie)
Centre for Innovation in Regulatory Science (CIRS)
Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ)
US Food & Drug Administration (leadership role in ABRF until 2021)
International Federation of Pharmaceuticals & Manufacturers Associations (IFPMA)
Foundation for Innovative New Diagnostics (FIND)

Advocacy Partners
AMA Treaty Alliance (AMATA)/IFPMA
Program for Appropriate Technologies in Health (PATH)
Yolse, Santé Publique & Innovation
Drug Information Association (DIA)

Funding Partners
Bill and Melinda Gates Foundation

Swiss Development Corporation (SDC)
World Bank
GIZ
The French Agency for Development

New partners (as of January 2022)
UNITAID (funding)
European Commission (funding)
USAID (funding, primarily through MTaPs and USP PQM+)
Susan Thompson Buffett Foundation (STBF) (funding)
Africa CDC (technical)
Africa Society for Blood Transfusion (technical)

Inactive Partners (as of January 2022)
Gavi The Vaccine Alliance
US Food and Drugs Administration (US FDA)

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