Strengthening regulatory systems in LMICs

Improving the sustainability of the vaccine innovation ecosystem in Africa

wellcome

Harris Access Consulting

Final compendium deck

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CRA Charles River Associates

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The aim of this project is to explore vaccines regulatory systems to improve the sustainability of the innovation ecosystem in LMICs

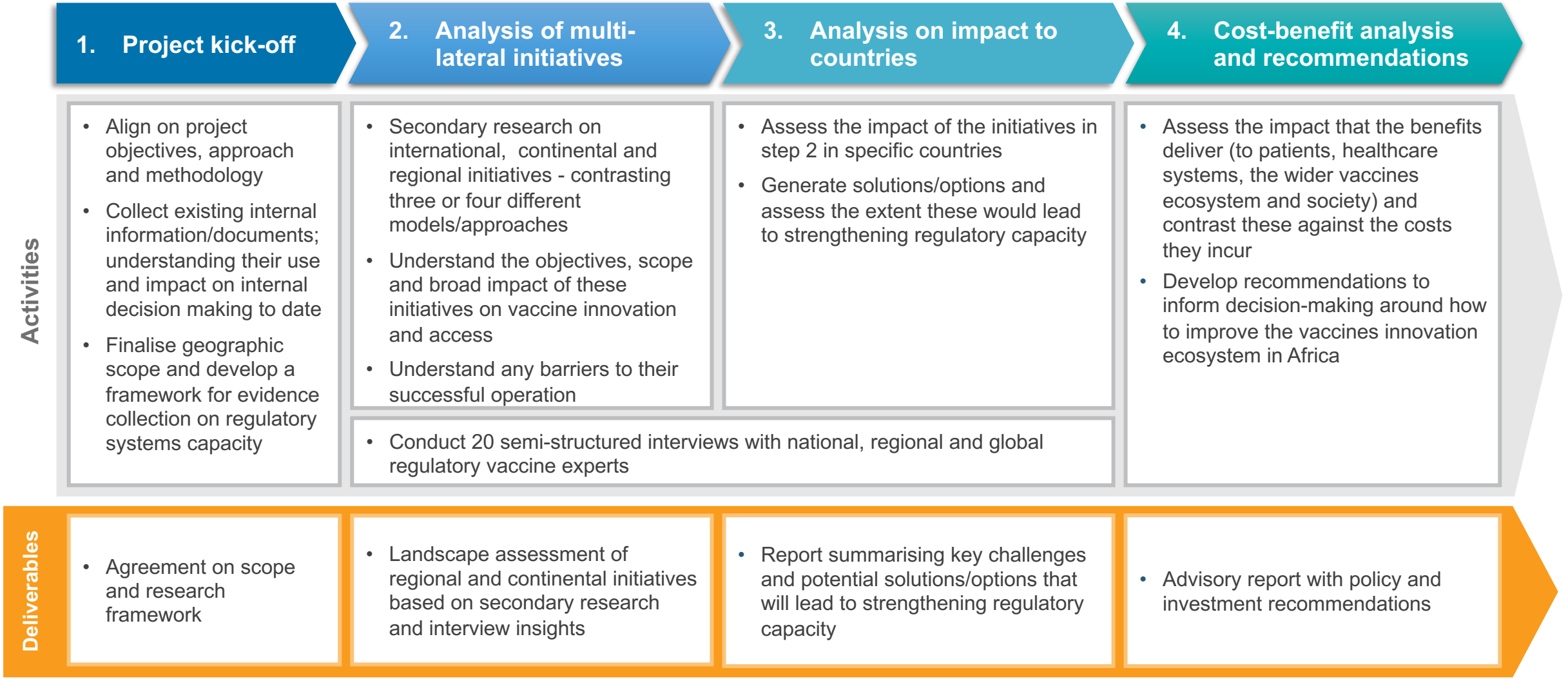
Overall project objective

To provide recommendations on future investments that will 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 public health

Specific objectives

1. Review existing regional and continental regulatory development programmes and initiatives for vaccines
2. Assess the cost-benefit of these regulatory proposals and initiatives in low- and middle-income countries (LMICs)
3. Prioritise recommendations on how Wellcome and other investors can best support regulatory strengthening initiatives in Africa

The project followed a four-phase approach



In step 2, a research framework was followed to enable collection of comparable data across multi-lateral initiatives

Area	Elements for analysis
1. Aims and background	• Date of initiation and rationale
	• Overall objectives and aspirations
	• Focus exclusively on vaccines vs all health technologies
	• Key stakeholders and donors
	• Participating countries
2. Activities conducted across the regulatory lifecycle	• Overarching regulatory focus areas (scope of activities)
	1. Facilitating research and development: Clinical trial regulation, ethic review, scientific advice, supporting innovation etc.
	2. Evaluating applications for approval: Recommendations for marketing authorisation, post-approval variations etc.
	3. Monitoring safety across the product lifecycle: Overseeing pharmacovigilance, post-marketing surveillance etc.
	4. Compliance and development of standards: Quality and GMP guidelines, GCP/GDP inspections, batch inspections etc.
	5. Disseminating information: International collaboration, HCP guidelines, patient information, industry engagement etc.
	• Key activities outside of the regulatory space (e.g., procurement)
3. Regulatory sustainability	• Extent that the initiative fosters R&D and public health innovation
	• Supports the local trade and manufacturing environment
	• Supports information sharing and reliance between NRAs
	• Supports harmonisation of standards
	• Embeds innovation and continuous improvement through regulatory science approaches
	• Has catalyzed any other initiatives
	• Changing from a donor-funded project to a self-sustaining initiative

Throughout the review, we identified gaps in literature for further testing in latter stages of research

Area	Elements for analysis
4. Evidence of impact	• Number of assessments undertaken
	• Impact on time measurements (e.g. clinical trial approvals or vaccine registration)
	• Uptake across participating countries and context-appropriateness of decisions at country level
	• Level of information sharing and transparency
	• Changes in maturity of participating NRAs
	• Notable vaccine examples
	• Evidence of any other targets or KPIs being met
5. Barriers to success	• Key challenges at initiative level
	• Key challenges at country level
	• External factors limiting progress and implementation

A range of sources have been reviewed for a comprehensive understanding of each of the initiatives

Our review draws from a range of sources:

1. **Public sources** including written articles, websites, conference materials, press releases from:
   - ***Academic literature*** e.g. assessment of the impact of initiatives, comparative review of regional initiatives
   - ***Government and public health agencies*** e.g. AUDA, NEPAD, WHO, PAHO
   - ***Industry and trade associations*** e.g. DCVMN, IFPMA
   - ***Grey literature*** e.g. local news outlets

2. **Discussions with external experts**

A range of stakeholders were interviewed to capture global, regional, national and industry perspectives

Stakeholder	Organization	Name	Role
Global	WHO	Samvel Azatayan	Team lead, RCN, REG, RPQ
	BMGF	Mac Lumpkin	Deputy Director Integrated Development / Global Regulatory System Initiatives Lead
		David Mukanga	Senior Program Officer Regulatory Affairs
	World Bank	Andreas Seiter	Global Lead Private Sector in Health, Nutrition and Population
	CEPI	Adam Hacker Malika Almansouri	Head of Global Regulatory Affairs (UK and NA) Leading regional efforts in Africa and the Middle East
	UNICEF	Shanelle Hall	Ex-Deputy Executive Director
	FDCO	Saul Walker	COVID response lead
	Gavi	Tiziana Scarnà	Senior Manager, Innovation and Special Projects, Market Shaping
Regional	AVAREF	Delese Mimi Darko	Founding member of AVAVREF, CEO Ghana FDA
		Bartholomew Dicky Akanmori	Regional Advisor, WHO AFRO
	CARPHA	Rian Marie Extavour	Technical Coordinator at Caribbean Public Health Agency
	PAHO / PANDRH	Analia Porras	Unit Chief, Medicines and Technologies, PAHO
	EDCTP	Michael Makanga	Executive Director
		Thomas (Tom) Nyirenda	Strategic Partnerships and Capacity Development Manager
	Africa Union / CDC	John Nkengasong	Director, also African Union Commission
	EMA	Emer Cooke	Executive Director
	APHRA	Helen Rees	Chairwoman, Chief Regulatory Officer
	AUDA-NEAPD	Paul Tanui Nancy Ngum	Senior Programme Officer Programme Officer
National	NAFDAC	Christianah Moji Adeyeye	Director General
	Ghana FDA	Delese Mimi Darko	CEO Ghana FDA
Industry	Merck (MSD)	Ginny Acha and Angelika Joos	Executive Director, Global regulatory policy
	IFPMA	Laetitia Bigger Sarah Adam Paula Barbosa	Director, Vaccines Policy Associate Director, Regulatory Affairs Associate Director, Vaccines Policy

Total 20

Once the regulatory challenges were categorized, we identified and prioritised opportunities for regulatory strengthening

Categorize challenges across the regulatory lifecycle

Identified and categorised key challenges across the regulatory lifecycle and cross-cutting factors impeding sustainability, drawing from interviews, desk research and expert advice*

Identify desired outcomes for regulatory strengthening

Based on the challenges identified across the regulatory lifecycle, identify the desired outcomes required for regulatory strengthening

Identify key outputs, activities and inputs required to achieve each outcomes

Identify the outputs, activities and inputs required to achieve the desired outcome, drawing from interviews and expert advice

Prioritise activities for funders

Prioritise activities based on key guiding principles and objectives for funders to consider in regulatory system strengthening

**Detailed slides included within the appendix*

Glossary of terms

Acronym	Definition
AE	Adverse event
AMA	African Medicines Agency
AVAREF	African Vaccines Regulatory Forum
AMRH	African Medicines Regulatory Harmonisation
AU	African Union
AU 3S	African Union Smart Safety Surveillance initiative on pharmacovigilance
CTC	Clinical Trials Community
CTs	Clinical Trials
EDCTP	European & Developing Countries Clinical Trials
EMA	European Medicines Agency
EUA	Emergency Use Authorisation
EUL	Emergency Use License
FDA	Food & Drug Administration (US)
GAVI	Gavi, The Vaccine Alliance
GDP	Good Distribution Practice

Acronym	Definition
GMP	Good Manufacturing Practice
GS-1	The Global Language of Business
MoH	Ministry of Health
NAFDAC	National Agency for Food & Drug Administration (Nigeria's National 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 Organisation

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A weak regulatory environment is detrimental to public health and patient safety

- **Poor availability of vaccines and medical products in Africa** has, in part, been attributed to weak and fragmented regulatory procedures, policies and systems in place
- The WHO estimates **at least 30% of national regulatory agencies (NRAs) have limited capacity to perform core regulatory functions** – this is substantially higher in Africa, where only four NRAs—Egypt, Ghana. Nigeria and Tanzania—have to-date attained WHO Maturity Level 3 for medicines, and only Egypt has recently achieved this designation for vaccines [1]
- The **absence of functional NRAs in any country** (i) exposes the population to potentially unsafe products of variable quality and effectiveness; (ii) facilitates the proliferation of substandard and counterfeit products; and (iii) prevents rational use, all of which contribute to poor health outcomes and lower life-expectancy
- 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
- The African Union and African CDC have established a partnership – Partnership for African Vaccine Manufacturing (PAVM) – with an ambitious target to reach the goal of **60% local vaccine production by 2040** [2]
- This offers an opportunity for those with an interest in Africa's public health and prosperity to consider opportunities for strengthening and accelerating regulatory system improvements

Sources in notes

Overview of existing regulatory reliance initiatives in Africa

- Several complementary national, regional and global initiatives have been introduced to **strengthen capacity, support regional harmonisation of regulatory policies**, and increase work-sharing and regulatory reliance
- According to the WHO, reliance is, “the act whereby the NRA in one jurisdiction may consider and give significant weight to—i.e. totally or partially rely upon—evaluations performed by another NRA or trusted institution in reaching its own decision. The relying authority remains responsible and accountable for decisions taken even when it relies on the decisions and information of others” [1]
- Most famously globally is the **WHO Prequalification (WHO PQ) programme** which assesses and prequalifies vaccines and active pharmaceutical ingredients, overseeing manufacturing standards for many of the multilateral programmes that procure and supply medical products to low-income countries in Africa
- In Africa, this most notably includes the **African Medicines Regulatory Harmonisation (AMRH)** and complementary capacity strengthening efforts with NRAs aiming to reach Maturity Level 3
- The vision for the future is to establish a continental body, the **African Medicines Agency (AMA)**, founded on the principles of reliance and convergence. The Agency will, if established as intended, help to facilitate coordination of selected regulatory activities and further harmonisation and cooperation across Member States, regional economic communities (RECs) and global reference authorities to support NRAs with oversight of medical products for routine and emergency use

Sources in notes

Multi-lateral initiatives investigated within the study (1/2)

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 (and now has been absorbed as one of the technical committees within the AMRH)

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) and active pharmaceutical ingredients (APIs) 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 on-going quality of pre-qualified products. Currently the central mechanism enabling countries to access donor-funded products, however the scope is limited to the highest priority 10% of products on the WHO Essential Medicines List (EML)

See appendix for detailed landscape assessment across multi-lateral initiatives

Multi-lateral initiatives investigated within the study (2/2)

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

The African Medicines Agency (AMA) – A new pan-continental agency aiming to provide regulatory advice to NRAs, enhance regulatory harmonisation and support access to relevant information and tools that support reliance

The African Regulatory Network (ARN) – Works in partnership with regulatory authorities to encourage greater harmonization and convergence of regulatory requirements

Africa Regulatory Taskforce (ART) – A joint effort established by the Africa Centres for Disease Control and Prevention (Africa CDC), the African Union Development Agency (AUDA-NEPAD)

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

See appendix for detailed landscape assessment across multi-lateral initiatives

The focus areas across initiatives and level of impact and uptake at country level identified by the literature review and interviews

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

Notes: Impact and uptake of efforts by the initiatives in each areas is based on the literature findings 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

Summary of critical enablers and limiting factors: AVAREF and AMRH

Initiative	Critical enablers	Key limiting factors	Potential solutions to key challenges
African Vaccine Regulatory Forum (AVAREF)	✓ **Consolidation of activities with AMRH** allows streamlining of process and broader outreach ✓ **Success in emergency context** e.g. Ebola vaccine demonstrates proof of concept ✓ **Best practice sharing/adoption of guidelines with key RECs** to leverage existing governance	× **Inconsistent implementation of 60 day deadlines** for reviews at the country level × **Activities limited to early stages of innovation pathway** in clinical trial applications × **Limited success in engaging Ethics Committees** to implement decisions × **Voluntary participation** at country level means benefits limited to those who are actively engaged	• **Leverage AMRH platform to engage all stakeholders** including RECs and ethic committees • **Enforce penalties for failure to meet timelines for review** e.g. 60 day for joint reviews
African Medicines Regulatory Harmonization programme (AMRH)	✓ **Leverages existing RECs** supporting regulatory cooperation and allowing for **existing harmonization activities to be built upon** ✓ **Establishment of regional centers of regulatory excellence**, supporting NRA capacity building and training ✓ **Encourages work-sharing and reliance through joint activities**, allowing each NRA to provide expertise and remain involved ✓ Supports **initiation of successful harmonization activities across RECs**, acting as a foundation for a continental wide initiative (the AMA)	× Extent to which each activity is conducted and **level of engagement/interest** in harmonization activities **varies across RECs** × Requirements for manufacturers to **submit an application and pay a fee each NRA** despite undergoing joint assessments/ inspections × **Inconsistent uptake** of joint activities or guidelines and **delays in NRA decisions** × **Lack of assurance and trust from NRAs** to support reliance activities × **Lack of a self-sustaining source of funding**	• **Establish a legal binding framework** which obligates NRAs to abide by joint decisions and enforce penalties for failure for NRAs to meet timelines • **Support further pairing/twinning activities with NRAs** to support reliance and work-sharing • **Increase transparency of the process**, inviting and responding to feedback from industry partners • **Establish a sustainable funding system** e.g. by charging industry user fees

Summary of critical enablers and limiting factors: PANDRH and PQ

Initiative	Critical enablers	Key limiting factors	Potential solutions to key challenges
Pan American Network for Drug Regulatory Harmonization (PANDRH)	✓ Technical work is **selected for the context and needs of NRAs** in a continuously updated project based approach ✓ **Projects are led by NRAs** themselves, supporting **reliance on NRAs of regional reference**, capacity strengthening and harmonization of standards ✓ **PANDRH conferences** provide a platform for **best practice and information sharing** amongst NRAs	× **Inconsistent use and adoption of technical documents/ recommendations** across member states due to differences in timing, quality and appropriateness × **Overlap of regional integration mechanisms** limiting harmonization due to differing strategic focuses × **Conflicts between** adopting global and PANDRH harmonization and **convergence mechanisms**	• **Streamline harmonization and convergence mechanisms in the region** to prevent conflicts of standards and priorities • **Improve timing and specificity of technical documents** to support uptake amongst member states
Prequalification (PQ)	✓ **Pre-requisite for 'functional' NRAs** encourage local capacity building in order to participate in PQ ✓ **Reliance on Collaborative Registration Procedure (CRP)** to enable information sharing with NRAs and reduce duplication ✓ **Sustainable financing model** through user based fees ✓ **WHO's wider system supporting activities** enable training and strengthening of NRAs	× **Inconsistent adherence to CRP requirements** for 90 day limit for approval at the country level × **Inconsistent uptake of CRP** (poor uptake in Latin America, Eastern Europe) × **PQ's scope restricted** to areas identified as a 'global health priority' and manufacturers perceive there is limited scope expand to other areas	• **Transparent communication and best-practice sharing for awareness building around CRP** across low uptake markets • **Encourage local country uptake** and capacity building to leverage spillover benefits to areas not included in WHO priority list

Summary of critical enablers and limiting factors: CRS and EDCTP

Initiative	Critical enablers	Key limiting factors	Potential solutions to key challenges
Caribbean Regulatory System (CRS)	✓ **Centered in an REC** supporting regulatory cooperation and allowing for existing governance to be leveraged ✓ **Reliance on reference authorities** allowing for efficiencies on the dossier review, standardization and faster market access ✓ **Operates on a user fee system**; potentially allowing for FTE sustainability (although MNF perceptions are currently unknown) ✓ Incentivizes industry through a **single point of entry** to countries	× **Lack of focus on vaccines** (due to coverage by the PAHO Strategic Fund) × **Lack of country-buy in and inconsistent legal frameworks** to facilitate uptake of CRS recommendations × **Activities are only limited to MA and pharmacovigilance** across the regulatory lifecycle × **Limited applications** from manufacturers due to inconsistent country uptake	• **Leverage external partners** (e.g. PAHO) for financing, training and mentorship • **Improve country participation and utilize legal authorities** to facilitate the rapid uptake of CRS recommendations, to ensure that the 60 timeline provided to NRAs for an MA decision is adhered to
European & Developing Country Clinical Trials Partnership (EDCTP)	✓ **Unique governance model** (of equal partnerships) strengthens participation and ownership from African partner ✓ **Partnership** with EU member states **supports reliance mechanisms and capacity strengthening** through training ✓ **Self-led strategic planning** of projects supports long term sustainability ✓ **Matched funding of prioritized activities** supports continuous improvement	× **Activities are limited to enabling the clinical trial environment** across the regulatory lifecycle × **Funding** is dictated by member state contributions which **may not be consistent** × **Lack of contribution and commitment** from some partners and/or conflicts with other initiatives × **Potential for poor grant management** for some of the activities	• Increase EDCTP **funding in regulatory harmonization activities** and **leverage partnerships to develop regulatory capacity** beyond clinical trials • **Support grant management** with additional training and technical assistance in project and financial management • **Leverage stakeholders** to promote EDCTP activities among political decision makers to support further alignment

Notes: SEARN, ARN and ART not included in the analysis due to limited information on impact and key performance metrics

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We categorized the challenges across the key steps of the regulatory lifecycle and cross-cutting factors impeding sustainability

Key steps of the regulatory lifecycle:

Factors impacting sustainability (cross-cutting the lifecycle):

- **Financing**
- **Individual human resources**
- **Institutional capacity**
- **Digital resources**
- **Legal, Policy and Governance environment**

Drawing on the current environment, some regulatory barriers are intervention specific across the regulatory lifecycle (1/2)

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 funding and collaboration between regulators and Research & Development (R&D) teams outside of pandemic and epidemic contexts to collaborate on CT design and assess interim data
- **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

For more details on the challenges, please refer to appendix slides 88-98

Note: Some challenges listed are not applicable in every case and there are exceptions to each case

Drawing on the current environment, some regulatory barriers are intervention specific across the regulatory lifecycle (2/2)

Manufacturing and quality assurance

- **Nascent technical know-how for oversight of vaccines and complex biologics.** 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 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
  - These gaps include lack of internet connectivity and insufficient laboratory equipment for testing
- **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

For more details on the challenges, please refer to appendix slides 88-98

Note: Some challenges listed are not applicable in every case and there are exceptions to each case

Others cut across the regulatory lifecycle (1/3)

Financing

- **Lack of autonomy and conflicting financing models dis-incentivize NRAs to harmonize or invest in capacity strengthening,** due to the lack of a defined distribution of funds when conducting certain processes
- **Limited industry incentive 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
- **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 needs, 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 harmonization activities

For more details on the challenges, please refer to appendix slides 88-98

Others cut across the regulatory lifecycle (2/3)

Institutional capacity

- **Only two of the continent's 47 NRAs (Ghana and Tanzania) have been designated Maturity Level 3,** meaning that reliance within the continent is nascent and dependent on external scientific and technical advice offered by SRAs and the WHO
- **NRA experience has been focused on the assessment, approval and registration of generic medicines** 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
- **Inconsistent professional recognition and workforce capacity** with rapid staff turnover, preventing the development and retention of expertise within NRAs
- **Uneven uptake of digital resources** to support efficiencies and workflow within NRAs, hindering effective uptake of reliance activities and undermining impact of decisions on medicines procurement
- **Performance monitoring by NRAs and AMRH REC initiatives is inconsistent**, undermining ability to track and report progress, identify weak spots, and communicate impact
- **Laboratory capacity is lacking**, preventing the regulatory community from providing adequate oversight to and support of local manufacturers

Digital resources

- **Varied digital infrastructure** to support effective convergence/ harmonization between countries and externally. When available, data is not always distributed between NRAs and other stakeholders, leading to information asymmetries

For more details on the challenges, please refer to appendix slides 88-98

Others cut across the regulatory lifecycle (3/3)

Legal and Policy environment

- **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.
- **Policies, procedures and practices within the RECs and NRAs that result in duplication of work done by Maturity Level 3 or 4 regulators or their equivalents**
- **Insufficient policy and legal framework to support reliance for lot release** based on a regional network-based laboratory model
- **Inability to rely on SRA opinions for non-localised epidemics**, leading to delays in authorisations for vaccines in emergency epidemic contexts
- **Unclear pathways for post-approval changes,** which can lead to supply shortages
- **Inconsistent political willingness** to participate in convergence/reliance due to misconceptions of loss of sovereignty, resulting in inconsistent uptake of regional recommendations and divergent and inefficient practices across countries; particularly problematic if legal basis is lacking for uptake of AMA recommendations/opinions
- **Vaccine hesitancy** due to limited communications resources to build public confidence on the regulatory approval of vaccines and limit the spread of vaccine misinformation to help facilitate access and uptake
- **Unclear pathway for how the AMRH initiative and the AMA will collaborate** to address the wider systemic, technical, legal, financial and policy challenges articulated above

For more details on the challenges, please refer to appendix slides 88-98

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Opportunities for investment can be grouped under three 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 +**

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 AMRH** joint secretariat and all components
- **Support the roll-out 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 roll-out 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 Systems** (R-IMS) 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 ■

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

Human Resources & Education

- **Develop comprehensive workforce strengthening strategy**
- **Identify the interdependencies** which impact workforce
- **Increase range and strategic value of RCORES**

Infrastructural

- **Roll out R-IMS 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

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 ■

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 ■

Appendix

Detailed landscape assessment

Multi-lateral initiatives investigated within the study (1/2)

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 (and now has been absorbed as one of the technical committees within the AMRH)

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) and active pharmaceutical ingredients (APIs) 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 on-going quality of pre-qualified products. Currently the central mechanism enabling countries to access donor-funded products, however the scope is limited to the highest priority 10% of products on the WHO Essential Medicines List (EML)

Multi-lateral initiatives investigated within the study (2/2)

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

The African Medicines Agency (AMA) – A new pan-continental agency aiming to provide regulatory advice to NRAs, enhance regulatory harmonisation and support access to relevant information and tools that support reliance

The African Regulatory Network (ARN) – Works in partnership with regulatory authorities to encourage greater harmonization and convergence of regulatory requirements

Africa Regulatory Taskforce (ART) – A joint effort established by the Africa Centres for Disease Control and Prevention (Africa CDC), the African Union Development Agency (AUDA-NEPAD)

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

AVAREF

AVAREF was established by the WHO with clear objectives in supporting the regulatory oversight of clinical trials conducted in the region

Aims and background	Current environment	Trends
Date of initiation and rationale	• In **2006**, the **World Health Organisation** (WHO) created the African Vaccine Regulatory Forum (AVAREF) [1] • There was an **increasing number of vaccine trial** candidates developed for diseases mainly endemic in Africa leading to a rise in the number of clinical trials planned in the region [1] • This was a growing **regulatory burden** for the countries as previously, they could rely on the vaccine producing country but there is no requirement for licensure on the producing country for vaccines **meant for use outside** their region	*No evidence to suggest any further discussion around the rationale for AVAREF*

Overall objectives and aspirations	• The key aims are to 1) **improve the regulatory oversight** of clinical trials conducted in Africa and 2) **promote harmonisation** of ethics and regulatory processes in the continent [2]
	  • In 2016, AVAREF **became one of the Continental Technical Committees** of the African Medicines Regulatory Harmonization Initiative [3]
	  • In April 2020, AVAREF published a **strategy and guidance for emergency preparedness** in response to COVID-19. The document guides ECs and NRAs on how to undertake expedited reviews and approvals of CTA and oversights of CTs during a pandemic [4]
		AVAREF has been active since its inception. In 2016, a new model and governance was proposed for AVAREF and its scope of work was extended beyond clinical trials for vaccines but to all medical products due to the pressing health needs on the continent

Focus exclusively on vaccines vs all health technologies	• AVAREF was initially established as platform to support the clinical trial applications of vaccine candidates [2] • In 2016, AVAREF's scope of work was broadened to cover not only vaccines but also **medicines** and **medical devices** [3]	*Provide support for broader medical technologies due to growing health needs*

Relevant as of April 2021; sources in notes

AVAREF was established through grants to WHO programs, following the inception the BMGF has been funding the initiative

Aims and background	Current environment	Trends

Key stakeholders and donors	• AVAREF currently has **four bodies** which govern the agency
	1. the Assembly which is the overarching body,
	2. Steering Committee (with representatives from the 8 RECs of the African Union) which defines policies, strategies & implementation
	3. Technical Coordination Committee made up of the local NRAs and ECs who provides scientific and technical advice and
	4. the Secretariat [2]
	• AVAREF is currently **funded** by the Bill and Melinda Gates Foundation though the initial establishment was also supported by the European and Developing Countries Clinical Trials Partnerships (**EDCTP**) and the Canadian HIV Vaccine Initiative (**CHIV**) [2]
	  • EDCTP contributed to the formation of AVAREF via **two grants to the WHO global training program** for regulators. 15 Francophone and 15 Anglophone regulators conceptualised the role of AVAREF and most members of the AVAREF Technical Advisory Committee were trained through the EDCTP ethics fellowship scheme
	  • The CHIV is an initiative in collaboration **between 5 Government of Canada agencies** to strengthen efforts to development of HIV vaccines. The Department of Foreign Affairs, Trade and Development Canada (DFATD) is one of the partnering agencies and they provided a **$2M grant to the WHO** to initiate AVAREF
	• AVAREF do not currently charge any fees for their services. [5] Donor support is the main source of funding though development partners through 'in-kind' support have also supported the initiative [6]
		None identified

Participating countries	• All 55 African countries are **eligible** to become members of AVAREF and all are **currently** members [2]	*None identified*

Relevant as of April 2021; sources in notes

Efforts have focused on facilitating R&D in the region, ensuring clinical trials applications are approved in a timely manner

Activities conducted	Description	
Overarching regulatory focus areas	• Support regulatory oversight of clinical trial applications in the region [1]	
1. **Facilitating research and development:** Clinical trial regulation, ethic review, scientific advice, supporting innovation etc.	✓	• AVAREF has developed three types of joint reviews which accelerate the timelines for clinical trial application reviews (regular within 60 days, expedited within 30 days and emergency within 10-15 days) [2]
2. **Evaluating applications for approval:** Recommendations for marketing authorisation, post-approval variations etc.	✗	• Out of AVAREF's scope
3. **Monitoring safety across the product lifecycle:** Overseeing pharmacovigilance, post-marketing surveillance etc.	✗	• Efforts directed at clinical trial application stage

4. **Compliance and development of standards:** Quality and GMP guidelines, GCP/GDP inspections, batch inspections etc.	✓	• The **clinical trial working group (CTWG)** was created from experts from the AVAREF's Technical Coordinating Committee representing NRAs and ECs from Burkina Faso, Ghana, Kenya, Malawi, Nigeria, Uganda and Zimbabwe on voluntary basis [3]
		  ◦ The group has developed standardised templates for **submission** and **assessment** of quality of clinical trials applications
		  ◦ The group was technically supported by experts from other regulatory agencies namely the Paul Ehrlich Institute. CEPI, BMGF, USFDA also provided input into the development of the documents
		• The **GCP working group** has also developed a clinical trials **inspection guide** and a checklist for **GCP inspections** [3]

Relevant as of April 2021; sources in notes

AVAREF's broader objectives in harmonization the ethics processes are still within the context of clinical trials

Activities conducted	Description	
5. **Disseminating information:** International collaboration, HCP guidelines, patient information, industry engagement etc.	✓	• Promoting awareness and continued political support from member countries and RECs was identified as a **key strategic direction** in the 2018-2020 **strategic plan** [1] • To ensure full adoption of the templates, they were presented to members of the **Economic Community of West African States (ECOWAS),** the **East African Community (EAC),** and **the Southern Africa Development Community (SADC)**, who reviewed and revised them [2]
Key activities outside of the regulatory space (e.g. procurement)		• AVAREF are involved in capacity building for **ethic committees**. In Dec 2020, AVAREF **initiated a partnership** with Multi-regional Clinical Trials (MRCT) Center where a training course was delivered to the AVAREF country-members' National Ethics Committees/Institutional Review Boards [3] • The key objective was to strengthen country members' understanding of ethical foundations of human participant research and their application to clinical research settings

Relevant as of April 2021; sources in notes

AVAREF have continually reacted to the changing landscape in Africa and since expanded their scope of work to cover medicines/devices

Regulatory sustainability	Description
Fosters R&D and public health innovation	• A key objective in the 2018-2020 strategic plan was to **stimulate innovation and research** in Africa, particularly for diseases which disproportionately affect Africans. Strategic direction 4 laid out a plan incl. a **product development platform** to track products of high value, a '**scientific advice' type service** for sponsors and **improvement** to the quality, transparency and predictability of regulatory activities [5] • To measure the success of this objective, AVAREF will monitor the number of products/technologies in clinical trials in which AVAREF's scientific advice contributed to the trial design [5] • Currently no indication of when next strategic plan will be released
Supports the local trade and manufacturing environment	• There is limited activity in this area however, AVAREF have developed a set of **standardized templates**, adopted in 2019, which include templates for NRA assessors to evaluate the **quality of manufacturing and control** (CMC) though in the context of a Clinical trial application (CTA) [3]
Supports information sharing and reliance between NRAs	• The AVAREF assembly organises the Biennal Scientific Conference on Medical Products Regulation in Africa and the African Medicines Regulatory conferences. The meetings bring together the **heads of national ethics committees** and **NRAs** to endorse the AVAREF regulatory tools and processes [1] • The AVAREF Secretariat also share best practices with the WHO regions globally and have presented to regulators in the Americas [4]
Supports harmonization of standards	• As part of the 2018-2020 strategic plan, AVAREF created **separate working groups** on clinical trials and good clinical practice inspections with the focus of creating standardised templates [2]
Embeds innovation and continuous improvement through regulatory science approaches	• *Current review suggests that published guidelines are relatively recent so there has been no call to update based on new scientific developments. To explore further in interviews*
Has catalyzed any other initiatives	• *TBD – limited public information on this, to explore further in interviews*
Changing from a donor-funded project to a self-sustaining initiative	• Since its inception, has been funded by donors

Relevant as of April 2021; sources in notes

AVAREF has successfully coordinated joint reviews within the agreed 60 days timeline though engagement is not uniform across the continent

Evidence of impact	Description
Number of assessments undertaken	• As of July 2020, AVAREF has coordinated **more than 10 joint reviews** (majority are vaccines) with an increasing number of developers submitting clinical trial applications though AVAREF [1]
Impact on time measurements (e.g. clinical trial approvals or vaccine registration)	• Although member states have agreed to timelines for clinical trial approvals, the Secretariat who monitors the timelines has identified that **not all member states are consistently meeting goals of 60 working days** due to differences in capabilities to assess the applications [5] • As of **2019**, AVAREF has achieved timeline reductions for trial approvals from 3.5 years to 60 days (for joint-review applications) [6]
Uptake across participating countries and context-appropriateness of decisions at country level	• All 55 member states of the African Union are member states of AVAREF however **North African countries have been less engaged** and AVAREF are working with WHO EMRO, AUDA NEPAD and the African Medicines Regulatory Harmonization Initiative to fully bring all the countries of EMRO into the AVAREF activities [7] • For example, at the local level **Egypt NRAs and EC** have not been fully engaged in all of AVAREF's activities • *TBD – limited public information on this, to explore further in interviews*
Uptake across participating countries	• In the past joint reviews, the **scope of countries** where clinical trials have been planned has ranged from **2 to 15 target countries [1]**
Level of information sharing and transparency	• *TBD – limited public information on this, to explore further in interviews*

Relevant as of April 2021; sources in notes

AVAREF has been critical in facilitating accelerated CT approval in times of health emergencies

Evidence of impact	Description
Changes in maturity of participating NRAs	• *TBD – limited public information on this, to explore further in interviews*
Notable vaccine examples	• Joint reviews of the **Ebola vaccine** clinical trial application in Geneva 2014, Tanzania 2015, Seirra Leone and Ghana in 2015 where AVAREF hosted meetings to facilitate the joint reviews [2] • Merck also approached AVAREF to use the **platform** for information sharing to facilitate an **accelerated registration of the vaccine**. AVAREF Secretariat also supported **the identification of experts** from the target countries to participate in the EMA, CP and WHO process. Ultimately, AVAREF contributed to the parallel regulatory reviews allowing the vaccine to receive an **approval within 90 days** of the WHO pre-qualification [3]
Evidence of any other targets or KPIs being met	• *TBD – limited public information on this, to explore further in interviews*

Relevant as of April 2021; sources in notes

Although the joint review process has proved successful, challenges have been identified in uniform information sharing across all countries

Barriers to success	Description
Key challenges at initiative level	• There is still **conflict** of joint review processes with some established local review processes [1] • The post-review process for final decisions are **not uniform [1]**
Key challenges at country level	• When used in emergency, there is **significant pressure** on NRA's resources due to the fast track mechanism used [1]
External factors limiting progress and implementation	• *TBD – limited public information on this, to explore further in interviews*

Relevant as of April 2021; sources in notes

AMRH

The AMRH was established to facilitate regional harmonization and capacity building, with the objective of improving access to medicines

Aims and background	Current environment	Trends
Date of initiation and rationale	• In **2009**, the **African Medicines Regulatory Harmonization programme** (AMRH) was created to address the **key challenges faced by NMRAs** in Africa that **ultimately hindered patient access to healthcare products**, including weak legislative frameworks, slow medicine registration processes and subsequent delayed approval decision, inefficiency and limited technical capacity [1]	• N/A
Overall objectives and aspirations	• The key aims of the program is to **create more effective, efficient and transparent regulatory mechanisms** through **regional harmonization and capacity building** across Africa to improve access to quality, safe and efficacious medicines [1],[2] • In 2017, AMRH global partners came to a consensus on the plan on implementation of phase 2 of the initiative to provide **end to end programme impact** in Africa from clinical trials authorization (CTA), registration of medical products and market authorization to safety surveillance of medical products [3]	• Aspirations of the AMRH has been to serve as a foundation for the **African Medicines Agency** (AMA) to oversee and co-ordinate the registration of priority health technologies across the continent [3]
Focus exclusively on vaccines vs all health technologies	• Although the immediate focus of the AMRH was on registering **generic essential medicines**, the initiative intends to gradually extend to other product categories such as **new chemical entities (NCEs), vaccines, medical devices and diagnostics** [3]	• To support scaling up the work of AMRH to **encapsulate all health technologies**, there are ongoing plans to create linkages with similar initiatives on regulation of medical devices and diagnostics, and blood products such as AVAREF, NOMCoL-SAA and Pan African Harmonization Working Party (PAHWP), coordinated by the NEPAD Agency through the AMRH Partnership Platform [4]

Relevant as of April 2021; sources in notes

The AMRH objectives are achieved through regional harmonization projects in already established Regional Economic Communities (RECs)

Aims and background	Current environment	Trends
Key stakeholders and donors	• The initiative was created by from a consortium of partners including **regulatory and political bodies**; New Partnership for African Development (NEPAD), the Pan-African Parliament (PAP) and the African Union Commission (AUC), **fund managers** (of the global medicines regulatory harmonization multi-donor trust fund (GMRH-MDTF)*:* the World Bank, **technical partners**: the WHO and Swissmedic, **donors**: BMGF, the UK Department for International Development (DFIPS) and Clinton Health Access Initiative (CHAI) [1] • Following initiation, the US Government/PEPFAR and IFPMA has funded the AMRH via the GMRH-MDTF and the Swiss Agency for Development and Cooperation (SDC) and the World Bank SWEDD contributing to the initiative outside of this fund [1] • To pursue the key aims of the initiative, the AMRH **launched regional Medicine Regulatory Harmonization (MRH) projects through Regional Economic Communities (RECs),** which are governed by an REC Steering Committee, with 2 representatives from each partner state and staff from the Secretariat, and a project co-ordination team with local staff from each NMRA [2],[3] • Additionally, the AMRH has established **Technical Working Groups (TWG)** on Regulatory Capacity Development, Policy and Regulatory Reforms and Expert Working Groups on GMP standards, composed of regulators and experts from AU Member States and RECs [3]	• In line with the aims to expand scope of the initiative and have a new governance framework of the African Medicines Regulators Conference (AMRC), **new Technical working groups (TWGs)** will be established under the AMRH Steering Committee on registration and pharmacovigilance which can be adopted by RECs and NMRAs and **existing networks will be transferred into continental TWGs** such as AVAREF for Clinical Trials, AMQF on Market Surveillance etc. [1], [4]
Participating countries	• The overall coverage of the AMRH initiative across the continent is more than 85% [3], with key MRH initiatives launched in **EAC** (pilot project launched in 2012), **SADC** (officially launched in 2014, however the Zazibona project was initiated between 4 NMRAs in 2013 and funded by DIFD), **ECOWAS** (launched in 2015), **CEMAC** (launched in 2016 under the OCEAC), **IGAD** (agreed and signed the call for Action to initiate implementation of a regional project since 2016) and **ECCAS** (although progress is still pending, the REC has shown political readiness)	• The plan for the AMRH was to have step-wise geographic expansion to cover all African countries through the AMA [2]

Relevant as of April 2021; sources in notes

AMRH activities span across the regulatory lifecycle, however the extent of each activity currently varies based on the priorities of the REC (1/2)

Activities conducted		Description
Overarching regulatory focus areas		• The **activities of the AMRH** focus on harmonizing policies and regulatory frameworks, enhancing human and institutional capacity, facilitating and coordinating research and knowledge management and effective alignment of regulatory activities with the AMRH framework and the AMA [1] • Medicine Regulatory Harmonization (MRH) projects aim to facilitate the objectives proposed by each REC, and therefore **the extent to which each activity is conducted currently varies based on REC specific priorities** • However, Phase 2 of the initiative is to ensure end-to-end impact with **activities across the regulatory lifecycle**, and the AMRH has already designated **11 regional centers of regulatory excellence (RCoREs)** to strengthen regulatory capacity development and academic/ technical training of the regulatory workforce in different regulatory functions [1],[2]
1. **Facilitating research and development:** Clinical trial regulation, ethic review, scientific advice, supporting innovation etc.	~	• Although not a key focus of existing MRH projects, RECs such as ECOWAS and OCEAC/ECCAS have outlined plans to support **local clinical trials and ethics committees** [2] • Additionally, consolidation of AVAREF under AMRH aims to strengthen clinical trials regulatory authorization and oversight in Africa through **harmonized requirements** for CTA/ethics committee approval and **development of guidelines for joint review** of clinical trial applications for vaccines and drugs candidates [2]
2. **Evaluating applications for approval:** Recommendations for marketing authorisation, post-approval variations etc.	✓	• A number of MRH projects have focused on supporting **joint dossier assessments** and generating **guidelines for harmonized medicines evaluations and registrations**, demonstrated across EAC, SADC/Zazibona and ECOWAS MRH projects, with similar work is underway in the OCEAC and IGAD [1]-[3] • The focus of these projects has been to implement **common technical documents and guidelines** for the registration of medicines, co-ordinate **joint dossier assessments** through work sharing via a common technical dossier format, and develop frameworks for mutual recognition [2]
3. **Monitoring safety across the product lifecycle:** Overseeing pharmacovigilance, post-marketing surveillance etc.	~	• Although not a key focus of existing MRH projects, RECs such as SADC and OCEAC/ECCAS have specified plans to **expand capacity into pharmacovigilance** (PV) and post marketing quality assurance, e.g. through a regional commission and drafting legislation to combat counterfeit medicines • Additionally, the AMRH aims to establish **a continental framework for sustainable capacity development on PV** in Africa which meets internationally recognized standards through harmonized requirements and guidelines[2] • In Phase 2, a **database of PV experts in Africa, regional expert working groups and an African PV Advisory Group** (APAG) will be established to ensure coordination of many of the fragmented PV initiatives [2]

Relevant as of April 2021; sources in notes

AMRH activities span across the regulatory lifecycle, however the extent of each activity currently varies based on the priorities of the REC (2/2)

Activities conducted		Description
4. **Compliance and development of standards:** Quality and GMP guidelines, GCP/GDP inspections, batch inspections etc.	✓	• Existing initiatives in the EAC, SADC, ECOWAS have focused on achieving **harmonized guidelines, requirements and standards** of GMPs and quality management systems within the NMRAs, and supported co-ordination of **joint and mutual recognition inspections** of manufacturing and testing facilities [1],[2] • Additionally, the NEPAD Agency, US Pharmacopeia and the West African Health Organization (WAHO) aim to transfer the network of medicine control laboratories in SSA (NOMCoL-SSA) into the African Medicines Quality Forum (AMQF) to reduce sub-standard and falsified medical products, complementing the existing work of the AMRH initiative through the AU Model Law [1]
5. **Disseminating information:** International collaboration, HCP guidelines, patient information, industry engagement etc.	✓	• As part of the EAC pilot MRH project, partner states aimed to implement a common information management system (IMS) for medicines registration in each NMRA [1] • AMRH RCoREs support information sharing through a database of regulatory experts for NMRAs to access, and encourage industry engagement by providing placements for NMRA staff within trainings [3]
Key activities outside of the regulatory space (e.g. procurement)		*No specific activities outside of the regulatory space have been identified*

Relevant as of April 2021; sources in notes

A key focus of the AMRH is to sustain the momentum created in regulatory strengthening and harmonization in Africa

Regulatory sustainability	Description
Fosters R&D and public health innovation	• Although there is currently limited activity in this area, the Phase 2 plan for the initiative aims **to encapsulate all areas of the regulatory pathway,** including facilitating research and development [1] • Through the AMRH programme, the NEPAD agency facilitated development of the AU Model Law on Medical Products regulation, which aims to ensure the promotion of innovation and access to new health technologies, one objective of which is ensuring that in countries involved in R&D, medical products that hold promise are developed, tested and scaled up for the improvement of the health impact [4]
Supports the local trade and manufacturing environment	• Activities within the AMRH focus on regulation of the manufacturing environment through harmonizing technical requirements and guidelines to build capacity in GMP inspections of manufacturing and testing facilities, and training in the licensing of manufacturers, importers, exporters, distributors and inspectors [1] • The AU Model Law also supports the AU's desire to promote local pharmaceutical production, with the goal of public health protection and economic growth [5]
Supports information sharing and reliance between NRAs	• Reliance between NMRAs is encouraged through the development of frameworks and guidelines that allow for the joint and mutual recognition of dossier assessments and inspections, which occur through work sharing and pooling of resources between NMRAs, to streamline the national level decision making process [1] • In 2013, the AMRH initiated the Binennal Scientific Conferences on Medical Products in Regulation in Africa (SCoMRA) as a **continental platform for sharing lessons learnt and best practices**, facilitating networking and collaboration, and rejuvenating actions towards sustaining momentum for regulatory strengthening and harmonization in Africa through strategic exchange of knowledge and ideas [1] • Lastly, RCoRE approaches such as twinning/ **staff exchange between NMRAs**, supports information sharing, strengthens relationships and builds confidence amongst NMRAs to conduct joint activities and recognize the work conducted by Partner States [2],[3]

Relevant as of April 2021; sources in notes

The success of the AMRH has catalyzed a number of initiatives and serves as a foundation towards establishing the AMA

Regulatory sustainability	Description
Supports harmonization of standards	• The key aim of the AU Model Law on Medical Products Regulation, is to provide the legislative framework for good medicine regulation at a national level, to **guide national governments and RECs to harmonize regulatory standards**, and to increase collaboration across countries. Currently the law has been taken up by 17 African countries, with an aim to have 25 adopting it by 2020 [1],[2],[3] • Within individual MRH projects such as the EAC, harmonization of standards has been shown through the implementation of the Common Technical Document and adoption of a supporting guidelines in all participating NMRAs [4]
Embeds innovation and continuous improvement through regulatory science approaches	• The RCoREs established by the AMRH contribute to **continuous improvement in regulatory science expertise**, providing technical training on the different functions, and spearheading operational research to pilot test innovations/interventions to inform best practices and promote scaling up activities [5]

Has catalyzed any other initiatives	• The AMRH has catalyzed a number of other initiatives, for example:
	  • The African Medicines Quality Forum (AMQF), established to address the challenge of prevalence of sub-standard and falsified medicines, supported by NEPAD, the WAHO and USP
	  • The Southern African Programme in Access to Medicines and Diagnostics, initiated by the SADC region [1]
	• Additionally, concrete achievements from the **AMRH have served as a foundation and catalyst towards establishing an African Medicines Agency** (AMA) [6]

Changing from a donor-funded project to a self-sustaining initiative	• The AUC leadership has called upon Member states to **prioritize investment of regulatory capacity development** to pursue the efforts towards convergence and harmonization of medical products regulation in RECs and to allocate resources for the operationalization of the AMA [3] • Although the harmonization initiatives are poised to transition from a donor funded pilot project (e.g. the EAC) to a **self sustaining permeant feature** of the African landscape, achieving a source of funding for this has been a challenge [7]

Relevant as of April 2021; sources in notes

The AMRH has been successful in harmonizing registrations and facilitating joint reviews in some RECs with reductions in approval times

Evidence of impact	Description

Number of assessments undertaken	• There has been a **significant increase in assessments across all medical products** undertaken by the RECs with MRH projects, however the number varies based on the REC and maturity of the MRH project;
	  • Since 2015, the EAC has conducted 10 joint product assessments, of which 83 medicinal product applications were considered and 36 of the products recommended by EAC Partner states [1]
	  • From 2013- 2019, the Zazibona initiative (within the SADC region) has evaluated 258 product applications with a final decision reached for more than 181 products (with 59% products receiving a positive response and 16% negative response) [6]

Impact on time measurements (e.g. clinical trial approvals or vaccine registration)	• Similarly, the marketing authorization review timelines across all medical products in the EAC and SADC region have **dropped by approximately 50%** [5]
	  • From 2012 - 2017, the timeline for national assessments in the EAC decreased from ~ 25 months to 8-14 months if the products were assessed through the new joint assessments process [1]
	  • From 2013- 2018, the mean time to recommendation for products evaluated by the Zazibona has been estimated at only 9 months [2]-[4]
	• Additionally, there have been improvements in joint acceptance and registration times (within 30 days) as well as total assessment times of only 240 days (150 days for regulators and 90 days for manufacurers, which is a marked improvement from the original timelines [6]

Uptake across participating countries	• Uptake amongst countries implementing an MRH project has been significant, with the EAC consisting of 7 NMRAs (represented by 6 countries) and the Zazibona initiative extending from 4 countries to 13 out of 16 countries participating within in scheme from the SADC region [6]
Level of information sharing and transparency	• During the process of joint dossier assessments, partner states took primary responsibility for different functions, requiring an in-depth level of transparency and information sharing [1] • However the lack of transparency regarding timelines and inadequate follow up from NMRAs has been noted as a key challenge within the EAC [7]

Relevant as of April 2021; sources in notes

The AMRH has been successful in harmonizing registrations and facilitating joint reviews in some RECs with reductions in approval times

Evidence of impact	Description

Changes in maturity of participating NRAs	• A number of key achievements have been made in changing the maturity of participating NRAs:
	  • Newer NMRAs such as South Sudan, Zanzibar and Rwanda have made significant strides in capacity to become semiautonomous NMRAs from only having departments or boards housed within their ministries of health to regulate medicines previously [2]
	  • Tanzania was the first NMRA in Africa to attain designation by the WHO as a maturity level of 3 (out of 4) which is denoted to agencies with “a stable and well functioning and integrated system of oversight for medical products” [1],[7]
	  • 4 out of 7 NMRAs in the EAC and 5 NMRAs in the ECOWAS are now 9001:2015 ISO-certified [9]
	  • 5 out of 7 NMRAs (72%) in the EAC are semi-autonomous and 10 out of 15 in ECOWAS have autonomous agencies that provide guarantee in the coordination and financing of regulatory activities in a country [9]
	• Additionally, the AMRH is instrumental in guiding NMRAs to **determine priority areas of action** for capacity strengthening and improvement [2]

Notable vaccine examples	• *TBD – to be validated further in interviews*
Evidence of any other targets or KPIs being met	• There has been significant progress on improving regulatory compliance and standards, with joint inspections and harmonized GMP certification being conducted by the EAC and SADC [8]

Relevant as of April 2021; sources in notes

The key challenge that remains within the AMRH initiative is the failure for NMRAs to recognize or leverage the outcomes from joint activities

Barriers to success	Description

Key challenges at initiative level	• Although harmonisation has been endorsed by heads of states across Africa (e.g. in the Model Law), a number of key challenges remain: [1]-[4]
	  • **Different levels of understanding, engagement and interest** in harmonisation of medicines regulation within RECs, with some making significant progress while others require more time and attention to achieve AMRH milestones
	  • **Poor communication** with technical partners about the scheduling of joint assessments
	  • Requirements for manufacturers to **submit an application and pay a fee to the NRMA in each partner state** despite undergoing joint assessments/inspections, which may **discourage manufacturers or importers** from registering their products
	  • Lack of a **self-sustaining source** of funding for some activities within the MRH projects in order to continue
	  • **Poor quality submissions and delays in submission of query applications**

Key challenges at country level	• Despite the progress made towards harmonization, challenges still exist in the outcome of the regional dossier review processes for national decision making processes by the NMRAs, such as: [4]-[6]
	  • **Delays in obtaining national registrations** once a joint recommendation has been made
	  • **Lack of a legal binding framework that requires partner states to recognize regulatory decisions** of their neighbors; to date only Zanzibar's NMRA recognizes the decisions of Tanzania's NMRA within the EAC
	  • **Lack of assurance and trust from NRAs** to recognize the quality of their newer peers assessments and inspections (and vice versa occasionally)
	  • **Staff turnover** in key leadership or technical roles, removing experience from the NMRAs
	  • **Lack of full leadership** from NMRAs which is critical for the sustainability of the initiatives

External factors limiting progress and implementation	• *TBD – limited public information on this, to explore further in interviews*

Relevant as of April 2021; sources in notes

PAHO

The Pan American Network for Drug Regulatory Harmonization was established by PAHO and NRAs to support regulatory harmonization

Aims and background	Current environment	Trends
Date of initiation and rationale	• Founded in 1902, the Pan American Health Organization (PAHO) is an international public health agency with a mission to strengthen national and local health systems and improve health outcomes in the Americas [1] • **PAHO has a number of strategies to support NRAs in improving access to high quality vaccines**, through the PAHO Revolving Fund for Vaccine Procurement, the Regional Network of Vaccines Quality Control Laboratories (RNVQCL) and coordinating several vaccine post-marketing surveillance initiatives [2] • Additionally, the **Pan American Network for Drug Regulation Harmonization** is an initiative established by the NRAs in the region and PAHO in 1999 to support the process of pharmaceutical regulatory harmonization in the Americas with the framework of national and sub-regional health policies [3]	

Overall objectives and aspirations	• PANDRH's mission is to promote **drug regulatory harmonization**, including such as aspects as quality, safety, efficacy and the rational use of pharmaceutical products, **while strengthening the capabilities of regional NRAs** [1], with objectives of: [3]
	  • **Strengthening regulatory functions and systems**, promoting cooperation and sharing among countries with the PAHO and with other regional and international organizations, civil society, industry associations and academia
	  • **Develop, approve and implement common proposals** (projects, joint activities, technical documents, guidelines, work plans, etc.) for the regulation of health technologies, taking into account international guidelines and standards for regulatory convergence
	  • Develop core competencies aimed at **supporting and strengthening good regulatory practices and regulatory science** in the Member States with the goal of achieving regulatory convergence in the Region. Encourage the NRAs of the Region to develop and maintain well-structured organizations to achieve effective regulatory functions as an essential part of health systems, in accordance
		None identified – to be verified further in interviews

Focus exclusively on vaccines vs all health technologies	• The focus of PANDRH can cover any area identified as a priority by the network across regulatory functions or cross-cutting themes, which included a specific vaccines working group with the objective of **harmonizing vaccine registration requirements in the region** [4]	• *N/A*

Relevant as of April 2021; sources in notes

Conferences held by PANDRH provide a key opportunity for stakeholders to discuss priority issues and disseminate decisions on harmonization

Aims and background	Current environment	Trends

Key stakeholders and donors	• The founding members of the Network are the NRAs, the trade associations and other health technologies in the region, the Latin American Federation of Pharmaceutical Industry (FIFARMA) and the Latin American Association of Pharmaceutical Industries (ALIFAR) [1]
	• The components of PANDRH include the: [1],[2]
	  • **Pan American Conference on Drug Regulatory Harmonization** (PANDRH), constituting a way to discuss priority topics in regulation and **disseminate the decisions on regulatory harmonization** of global initiatives (e.g. the International Conference on Harmonization). Members include all the regions drug regulatory authorities, as well as representation of organisms for economic integration (e.g. CARICOM and MERCORSUR), academics, professional/ manufacturer associations, civil society and other groups interested from all the continent sub-regions based on the conference topic
	  • **The Steering Committee (SC**), as the **decision making body for the strategic and operational management of the network**, and making recommendations for evaluation and discussion at the conferences. Members include the Secretariat, members appointed and designated to represent each sub-region of the Americas (with 4 year rotations) and select representatives regional reference NRAs, regional regulatory initiatives and associations of producers of health technologies as well as FIFARMA and ALIFAR (as founding members)
	  • **The Secretariat** – providing technical and administrative support to PANDRH, done by PAHO
	  • **Technical Working Groups (WGs)** in the areas considered as priority by the Conference consisting of experts, with academics and representatives from each regional bloc if possible [1]
		• The 2014-2020 Strategic Plan outlines the need for **a new governance structure** which should facilitate the participation of relevant members and provide **reports of the existing working groups and a proposal for their continuation** [4]
		• The technical work conducted by PANDRH will occur through the development of **projects** proposed by any of the members of the network in priority areas based on **a systematic analysis of the context and needs of NRAs** in each country biannually [3]
		• The strategic areas will then be defined by an approved **prioritization methodology** and will be coordinated by an **NRA of regional reference** and other representatives, with **the Steering Committee monitoring the development of the projects** through regular reports by the leaders [3]

Participating countries	• Representatives from each of the following regions can be appointed for the PANDRH Steering Committee from North America, Central America, the Caribbean, Andean Region and the Southern Cone (see notes for country breakdown) [2]	

Relevant as of April 2021; sources in notes

PANDRH activities span across the regulatory lifecycle in areas identified as a priority by the network

Activities conducted		Description
Overarching regulatory focus areas		• PANDRH supports **regulatory harmonization processes across the regulatory lifecycle**, while **strengthening the capabilities** of the regions NRAs in the region's countries and **promoting reliance** among them [1] • The **13 Technical Working Groups** established **conduct diagnostic studies to identify the differences** regarding implementation of international standards, define the necessary **strategies for technical cooperation**, analyze international guidelines and experience of NRAs in the region, develop educational tools and **prepare harmonized proposals** in their areas considered during the conference for implementation in the region [3] • The working group system has now switched to a project based approach in which similar activities are conducted but projects put forward are approved by the steering committee based on their potential to **contribute to regulatory convergence** and strengthen regulatory capacities, and **are lead by an NRA of regional reference** with the support from steering committee to **ensure adequate implementation of guidelines and decisions** [3]
1. **Facilitating research and development:** Clinical trial regulation, ethic review, scientific advice, supporting innovation etc.	✓	• PANDRH has established working groups on **Good Clinical Practice (GCP)** which have developed harmonized guidelines for NRAs on the authorization and monitoring of clinical trials and to assist researchers, ethics committees and universities and companies in conducting and evaluating this research [4] • Additionally, the **PANDRH Vaccines Working Group** worked to harmonize the requirements for the authorization of clinical trials of vaccines in their different phases and monitor their implementation [5]
2. **Evaluating applications for approval:** Recommendations for marketing authorisation, post-approval variations etc.	✓	• The PANDRH Vaccines Working Group has developed technical documents on harmonizing guidelines and requirements for the **licensing and registration of vaccines**, and have monitored their implementation across NRAs [5] • Additionally, through technical documents and recommendations the **Registration of Medicines working group** worked on promoting and facilitating the harmonization of regionally recognized and appropriate technical criteria for **medicines registration** [6]
3. **Monitoring safety across the product lifecycle:** Overseeing pharmacovigilance, post-marketing surveillance etc.	✓	• The PANDRH Pharmacovigilance Working Group has produced technical documents on **Good Pharmacovigilance Practices,** detailing the methods, tools, training and educational activities that should be used to support harmonization of pharmacovigilance in the region [7] • Additionally, the Vaccines Working Group promoted the establishment of surveillance systems for Events Supposedly Attributed to Vaccination or Immunization (ESAVI) [5]

Relevant as of April 2021; sources in notes

In addition to PANDRH activities, the PAHO Vaccine Revolving Fund supports NRAs through the pooled procurement of vaccines

Activities conducted		Description
4. **Compliance and development of standards:** Quality and GMP guidelines, GCP/GDP inspections, batch inspections etc.	✓	• The PANDRH Good Laboratory Practices Working Group has developed several technical documents to **guarantee the quality of laboratory test results and facilitate mutual recognition of the results** [1] • The PANDRH Good Manufacturing Practices Working Group developed technical documents on GMP and raising the level of NRA leadership in the implementation and monitoring of it in each country [2] • Additionally, the Vaccines Working Group aimed to harmonise the requirements of GMPs specific to vaccines and monitor their implementation [3]
5. **Disseminating information:** International collaboration, HCP guidelines, patient information, industry engagement etc.	✓	• The PANDRH Working group on **Medicines Promotion** developed ethical criteria for promoting advertising and publicizing pharmaceuticals [1]
Key activities outside of the regulatory space		• PAHO supports access to vaccines outside of the regulatory space by the **Vaccine Revolving Fund through pooled procurement,** thereby ensuring continuous and faster access to vaccines at an affordable price [4] • For access to COVID vaccines, PAHO has additionally been involved in supporting implementation of information systems, training of healthcare workers, generating vaccine demand and guiding risk and strategic communication strategies and tools [5] • Through these activities, PAHO has established a direct line of communication with health authorities making decisions on immunization programmes and has a technical team which can support with evaluation of the cost-effectiveness and technical preparations necessary for introduction of new vaccines [6]

Relevant as of April 2021; sources in notes

PANDRH's activities and technical documents have played a key role in the harmonization of standards and capacity building

Regulatory sustainability	Description
Fosters R&D and the innovation ecosystem	• Research and development is fostered through PANDRH working group efforts on Good Clinical Practice, which support NRAs in conducting and evaluating clinical trials [1]
Supports the local trade and manufacturing environment	• Efforts from the Good Manufacturing Practices working group aims to support the local manufacturing environment, and including technical experts representing the industry during the development of technical documents allows for a constructive dialogue to be established with NRAs, and guidelines/proposals that are feasible to be implemented within the local trade and manufacturing environment [1] • Lastly, the dissemination of standardized country regulations has supported the establishment of institutional, bilateral and multilateral cooperation agreements that are aimed at strengthening and improving international trade [1]

Supports information sharing and reliance between NRAs	• The working groups have produced multiple guidelines in their areas of interest aimed at **strengthening the countries regulatory capacity** through: [1]
	  • Development of human resources
	  • Generation and sharing of knowledge about drug regulation in support of criteria development and decision making
	  • The sharing of experiences between the NRAs and other PANDRH members and providing a platform to discuss common problems and search for solutions, ultimately supporting collaboration and information sharing
	  • Implementation and adoption of PANDRH's technical standards at the national level
	• Additionally, the Vaccines Working group aims to support convergence and recognition of vaccine regulation systems among NRAs of the region, and generate and organize tools and training activities aimed at NRA personnel [3]
	• PANDRH also facilitates **generation and exchange of information** between NRAs through leveraging the Regional Platform on Access and Innovation for Health Technologies (PRAIS), thereby enhancing the quality of regulatory activities with fewer financial, logistical and human resources [1]
	• Additionally, due to the involvement in establishing PANDRH reference NRAs, technical cooperation is supported where more developed NRAs share knowledge and experience with less developed NRAs [1]

Supports harmonization of standards	• PANDRH's key objective is to support the **harmonization/ convergence of standards** through dialogue, working groups and the development of technical documents, in addition to supporting their implementation and training in these activities [1] • These documents and activities have played a key role in building capacity in regions countries and are important references in the preparation of national standards and in the training of human resources at the national regulatory authorities [1]

Relevant as of April 2021; sources in notes

Through use of the network, countries have established new pathways to exchange ideas and experience

Regulatory sustainability	Description
Embeds innovation and continuous improvement through regulatory science approaches	• The continuous evaluation of projects which address the needs and context of NRAs demonstrates the prioritization of continuous improvement amongst PANDRH's activities • Additionally, a key area highlighted within the 2014-202 strategic plan is to promote the development and application of regulatory science in decision making processes to support the strengthening of NRAs and regional regulatory convergence [1]
Has catalyzed any other initiatives	• Through use of the network, countries have established numerous pathways and forums to exchange ideas and having discussions, e.g. the Network of Official Medicines Control Laboratories (OMCL) has been established to discuss knowledge and experience of medicines quality control between experienced bodies (e.g. regional reference laboratories/ those who have been pre-qualified by the WHO) and those less advanced bodies [1]
Changing from a donor-funded project to a self-sustaining initiative	• PANDRH is financially supported by PAHO/WHO, but additional funds come from governments, the pharmaceutical industry, international organizations and registration fees from training courses [3]

Relevant as of April 2021; sources in notes

Although a number of technical documents have been developed, the level of use and adoption varies amongst member countries

Evidence of impact	Description
Number of assessments undertaken	• *Limited public information – to be verified further during interviews*
Impact on time measurements (e.g. clinical trial approvals or vaccine registration)	• *Limited public information – to be verified further during interviews*

Uptake across participating countries and context-appropriateness of decisions at country level	• In 2014, when analyzing the adoption of PANDRH's harmonized requirements for the licensing of vaccines, it was shown that out of 19 countries 15 have specific requirements for the registration of vaccines, in which 21 % fully adopted and 37% partially adopted the PANDRH technical document [1]
	  • Reasons for not adopting the requirements included availability of regulations based on other harmonization initiatives, having existing regulations in place or do not currently have specific regulations on it, which can still have an impact on time and resources required for dossier development [2]
	  • Additionally, some NRAs reported use of the technical document informally to oversee regulatory processes before formal adoption [2]

Level of information sharing and transparency	• Despite some countries not adopting the PANDRH framework, there is still a level of convergence of standards due to the active participation and information sharing conducted between participants of the working groups from member states [2]
Changes in maturity of participating NRAs	• *Limited public information – to be verified further during interviews*
Notable vaccine examples	• *Limited public information – to be verified further during interviews*
Evidence of any other targets or KPIs being met	• *Limited public information – to be verified further during interviews*

Relevant as of April 2021; sources in notes

Despite improvements in regulatory capacity, difficulties with regional integration and uptake of standards amongst NRAs remains a challenge

Barriers to success	Description

Key challenges at initiative level	• Within the 2014-2020 strategic plan, a number of key issues were highlighted including: [1]
	  • **Difficulties with regional integration limiting harmonization** – as there are multiple integration mechanisms available within the region (e.g. CARICOM, Andean Community of Nations etc) which are geographically defined, some members participating in more than one with a different strategic focus with regards to regulation of medicines
	  • **Conflicts** amongst members between **adopting global and PANDRH harmonization and convergence mechanisms** (e.g. ICH, the Asia-Pacific Economic Cooperation forum and International Medical Regulators Forum)
	  • **Lack of awareness of the networks activities** and who the representing members on the steering committee are, as there was no established communication mechanism between countries
	  • **Lack of a defined criteria** for preparing PANDRH's technical standards

Key challenges at country level	• Additionally, a number of challenges at country level have been noted which include: [1]
	  • **Lack of implementation of PANDRH's recommendations/ guidelines**, as countries are not obliged to implement them and timing, quality and appropriateness of the guideline may influence the uptake. [2] In 2015, results indicated that 61% of technical documents produced by PANDRH have been used for the development of NRA regulations, with 34% fully adopted and 27% partially adopted, with lack of adoption due to existing standards or harmonization with other initiatives [1]
	  • Some technical documents were considered **too general and lacking on specific guidance** and some member states may not wait for PANDRH to issue a technical document to update their regulations[2]
	  • **Lack of human resources** to assume roles for a specific task (in regulatory research and training of experts), and the lack **of specific technical competencies** to ensure effective implementation of harmonized standards
	  • **Lack of a sustainable response to training** to ensure that NRAs can perform their regulatory functions applying up to date regulatory science and good regulatory practices
	  • **Lack of infrastructure** of compliance with specific requirements (e.g. GMP) and for systematization and follow up actions

External factors limiting progress and implementation	• *No specific information identified – to be verified further in interviews*

Relevant as of April 2021; sources in notes

WHO Prequalification (PQ)

PQ was established to ensure products for the UN procurement agencies reached the quality, safety and efficacy standards of the WHO

Aims and background	Current environment
Date of initiation and rationale	• The Prequalification (PQ) Programme is provided by the WHO to facilitate access to medicines which **meet standards of quality, safety and efficacy for high priority areas in low and middle income countries**. The vaccines prequalification program was launched in 1987 [1] • In 1974, vaccines were increasingly produced and products were bought by the UN procurement agencies – UNICEF and Pan American Health Organization Revolving Fund (PAHO RF). The agencies were conscious of the need to ensure the quality, safety and efficacy of the products and so in 1987, UNICEF established an agreement with the WHO to request involvement in assessing these criteria [5]

Overall objectives and aspirations	• The key purpose of PQ is to ensure good quality, safe and efficacious products are procured and distributed [3]
	  ○ The **service is for all UN procurement agencies** (started with UNICEF only) [4]
	• PQ for vaccines covers **standards related to manufacturing, licensing, quality control, labelling, transportation and storage of vaccines** [5]
	  ○ Investigation of safety-related complaints are carried out by WHO teams working in vaccines safety
	  ○ Vaccines regulatory strengthening is part of the broader support offered by WHO to NRAs through systems supporting activities

Focus exclusively on vaccines vs all health technologies	• The PQ programme covers immunisation devices, in vitro diagnostics, medicines, vaccines, vector control products and inspections services. Each product stream has their **own activities** [2] • Vaccines PQ is to **support the specific needs of national immunisation programs** regarding vaccine characteristics such as potency, thermostability, presentation, labelling and shipping conditions. It covers all vaccines required for routine immunisation against priority diseases. Priority is determined by WHO with UNICEF and the Revolving Fund of PAHO dictated by 4 key criteria 1) demand in UN-supplied markets 2) suitability for WHO needs 3) recommendations by WHO's Strategic Advisory Group of Experts and 4) supply security [2]

Relevant as of April 2021; sources in notes

PQ's main source of funding comes from fees charged directly to manufacturers but also through ad hoc donations

Aims and background	Current environment
Key stakeholders and donors	• From the outset, vaccines PQ was funded by UNICEF alone by levying a small percentage on each purchase order. In 2017, a new financing model was implemented which **charges a fee directly to the vaccine manufacturers which will generate at least 50% of the funds requires to ensure operation** [5] • Other ad-hoc contributions includes Bill and Melinda Fates Foundation, USAID and some national governments such as Netherlands [3] • The national regulatory agencies (NRAs) and national control laboratories (NCLs) play a vital role in regulatory oversight, testing and release of the vaccines [2]
Participating countries	• Vaccines PQ may **assess any vaccine that is a WHO priority** [4] • The **local NRA of the vaccine producing country must be assessed through the WHO Global Benchmarking Tool** and it must be deemed 'functional' achieving a maturity level of 3. Once the local NRA achieves this pre-requisite, the local manufacturers in that country are eligible to apply for PQ [4]

Relevant as of April 2021; sources in notes

PQ indirectly contributes to local regulatory strengthening due to minimum requirements on NRA maturity to participate in the program

Activities conducted		Description
Overarching regulatory focus areas		• PQ offers **indirect strengthening of NRAs through incentivizing development and capacity building**. This is because PQ will only accept submissions from vaccine manufacturers if the NRA of the producing country has been assessed as 'functional' against the indicators defined in the WHO assessment tool [2]
1. **Facilitating research and development:** Clinical trial regulation, ethic review, scientific advice, supporting innovation etc.	~	• The PQ team leverage strong partnerships with donors, manufacturers and local NRA to support the ecosystem for product development. In general PQ is seen to enable tailoring of products to the LMIC specific context [5]
2. **Evaluating applications for approval:** Recommendations for marketing authorisation, post-approval variations etc.	✓	• A major revision of the vaccines PQ was adopted in 2010 and came into force in 2012. The revised process provides the option for fast-tracked assessment if the WHO has an official agreement for information sharing with a NRA [2] • PQ ensures vaccines meet the needs of the NIPs in target countries including programmatic suitability, suitability for co-administration and relevance of clinical data to the target population. With these, the countries importing WHO prequalified vaccines could leverage the prior evaluations to enable an expedited vaccine registration (if they have the official agreement for information sharing) [4] • Through the Collaborative registration procedure (CRP), NRAs commit to reaching a decision within 90 days of receiving access to WHO's data submitted for PQ. This is currently only available for medicines but has proved successful in improving the efficiency of NRAs. The procedure is currently being piloted with select vaccines and diagnostics [5]
3. **Monitoring safety across the product lifecycle:** Overseeing pharmacovigilance, post-marketing surveillance etc.	✓	• WHO is responsible for post-prequalification activities including monitoring product quality, safety and conducting a targeted testing program. ○ If there are quality concerns, the supply of prequalified vaccines can be suspended or it is delisted from the PQ list as part of WHO's ongoing monitoring efforts [2]
4. **Compliance and development of standards:** Quality and GMP guidelines, GCP/GDP inspections, batch inspections etc.	✓	• In the 1996 revision, adherence to GMP was introduced to the PQ process [3] • Key principles in the process include understanding production process and quality control methods, producing consistency through GMP compliance, testing consistency of lots as well as monitoring complaints from the field. WHO will conduct site audits at the manufacturing facilities with observers from the responsible NRA [6]

Relevant as of April 2021; sources in notes

Best practice sharing is conducted through the WHO platform for co-development of standards

Activities conducted	Description	

5. **Disseminating information:** International collaboration, HCP guidelines, patient information, industry engagement etc.	✓	• **PQ uses two strategies to promote implementation of WHO norms and standards for vaccines** [3]
		  • WHO Member states are invited to participate in expert meeting to develop WHO standards focusing on the review of scientific evidence clinical evaluation of vaccines. Through this, the participating regulators acquire the specific expertise to drive the implementation of agreed standards activity in their own environments [3]
		  • WHO also organises implementation workshops for new WHO standards using practical examples and case studies – priority topics include vaccine lot release, stability evaluation, safety of call substrates for vaccine production and Good Manufacturing Practice (GMP) [3]

Key activities outside of the regulatory space (e.g. procurement)		• **PQ is largely a program to support procurement**. In LMICs, most vaccines procurers rely on WHO PQ products exclusively (such as GAVI and UNICEF) which supplies two thirds of the total donor funded vaccines for LMIC [2] • PQ also undertakes risk-based assessment of products during public health emergencies of international concern called Emergency use listing. This has included Ebola and Zika virus and also COVID-19. The risk based assessment is carried out on behalf of procurement agencies when prequalified or stringently-approved products are not yet available or not available in sufficient quantity [1]

Relevant as of April 2021; sources in notes

PQ enforces established WHO norms and standards; the program has significant impacts on the local manufacturing capacity

Regulatory sustainability	Description
Fosters R&D and public health innovation	• Perceptions are that PQ have had a key impact in enabling product innovation that is context relevant for LMICs which normally cannot be assessed through a local NRA [5]
Supports the local trade and manufacturing environment	• PQ has raised manufacturing standards in LMICs; representing around 50% of the manufacturers with prequalified vaccines. Moreover, there are also spillover effects when the manufacturers use the same standard to produce non-prequalified products [1] • Moreover, national control laboratories producing prequalified vaccines ae eligible to become full members of WHO-National Control Laboratory Network for Biologicals. This gives them access to the network's information sharing platform [4]
Supports information sharing and reliance between NRAs	• **There are 4 types of inspection-related capacity building activities to support local NRAs:** 1) training of local in-country NRA inspectors; 2) participation of NRA inspectors in WHO inspections; 3) Rotational inspector program at WHO HQ; and 4) invitation of ex-rotational NRA inspectors as co-inspectors [6] • This decision to restrict applications from manufacturers where the local NRA is deemed 'functional' was implemented in 2002 and has been identified as WHO's greatest impact in strengthening the capacity of NRAs in developing countries [7]
Supports harmonization of standards	• WHO first published a **guideline** on national control of vaccines in 1981 where it recommended the establishments of NRAs [3] • There was further refinement in the guidance to develop NRAs through the concept of 'vaccines of known good quality'. This means that 1) the NRA independently controls the quality of the vaccine in accordance with the 6 specific functions defined by WHO and 2) there are no unresolved confirmed reports regarding quality problems
Embeds innovation and continuous improvement through regulatory science approaches	• Vaccines PQ has gone through several rounds of revision since its inception in 1987. The last update was made in 2010 and since 1987, the scope of activities has only increased. Measures have been implemented to strengthen the procedure for example, improved communication and transparency through web list, fast track approaches for times of emergencies [8]
Has catalyzed any other initiatives	• WHO advocates the use of Collaborative Registration Procedure (CRP) for prequalified vaccines. This is report-sharing procedure in which evaluation reports and test results from WHO contracted laboratories and reports of site inspections are shared with interested NRAs. A signed agreement is required [5]
Changing from a donor-funded project to a self-sustaining initiative	• In 2017, WHO put in place the latest financing model aimed at creating a more sustainable source of financing through a new fees-based model for the manufacturers of the prequalified medicines and vector control products [2]

Relevant as of April 2021; sources in notes

Through the collaborative registration procedure, NRAs are able to accelerate the local approval through information sharing with WHO

Evidence of impact	Description
Number of assessments undertaken	• As of March 2021, ~159 vaccines have been prequalified [1] • The number of vaccine types included in the portfolio has increased from 6 in 1986 to 33 in 2012. [3] In 1987, only 2 diseases were covered by PQ and since then the scope is now covering 20 disease areas [2].
Impact on time measurements (e.g. clinical trial approvals or vaccine registration)	○ Since its launch in 2013, the Collaborative registration procedure (CRP) for medicines has expanded to 34 countries (mostly Sub-Saharan Africa) and the number of registrations increased from 15 to 123 between 2015-2017 ○ However, only about 50% of the registrations in 2017 met the 90 day time limit imposed on NRAs for approval timelines • Data suggests that NRAs relying on CRP have achieved significant acceleration in approval timelines. Pre-CRP, the NRA approval times where ~330 days for novel drugs and ~550 days for generics. In 2018, the average was 78 days with the use of CRP [2]
Uptake across participating countries and context-appropriateness of decisions at country level	• There is growing appetite for PQ and a growing number of manufacturers with at least one pre-qualified vaccine. The data suggests that the higher the income level of the country, the lower the number of vaccines prequalified per manufacture. In 2018, developing country manufacturers (DCM) prequalified 7.5 vaccine products when a multi-national corporation (MNC) manufacturer prequalified only 4.5 [2]
Level of information sharing and transparency	• *TBD – limited public information on this, to explore further in interviews*

Relevant as of April 2021; sources in notes

PQ has enabled over 2M in sales in vaccines in low and middle markets, facilitating access to safe and quality controlled products

Evidence of impact	Description
Changes in maturity of participating NRAs	• Between 1997-2019, WHO has trained more than 8000 NRA staff worldwide, the number of 'functional' NRAs have increased by 70% during this period [1]

Notable vaccine examples	• **MenAfriVac (Meningococcal A conjugate vaccine)** [1]
	  • WHO conducted the PQ using a fast track procedure in less than 6 months and several other key activities from WHO supported the in-country registration by local NRA. WHO spearheaded the international efforts to develop a vaccine in record time (5 years) at a tenth of the cot of typical new vaccine, expedited the licensure through the WHO facilitate collaborative process and supported NRA in India through a parallel process with Health Canada on the assessment, inspection and other regulatory processes
	• **Inactivated Polio Vaccines (IPV)** [1]
	  • WHO PQ prequalified 6 IPVs since 2005 to support innovation and ensure there is sufficient supply of IPV to prevent reintroduction of poliovirus

Evidence of any other targets or KPIs being met	• PQ has enabled a large donor-funded market size of approximately USD 3.5 billion of quality, safe and efficacious products across all product streams though the majority comes from vaccines (USD 2.143M) [1] • In Malaria and 1st line TB, PQ has enabled 90% of market access in total value, 51% of HIV-ARVs are WHO prequalified [1]

Relevant as of April 2021; sources in notes

Despite tools in place to accelerate NRA timelines, compliance at the country level requires improvements

Barriers to success	Description

Key challenges at initiative level	• Several barriers in external communication have been identified which hinder the impact of the PQ team and systems-supporting activities. Improvements in communication would enable a large impact on guiding innovation and early stage development. Key areas of poor transparency include: [1]
	  • PQ application process
	  • LMIC relevant innovation support

Key challenges at country level	• Although CRP enables streamlining of the NRA approval, full compliance has not been achieved. Imbalances between countries mean that the benefits of CRP are not able to come to fruition in terms of the accelerated time to approval. Many countries do not adhere to the 90 day limit imposed on them [1]
External factors limiting progress and implementation	• *TBD – limited public information on this, to explore further in interviews*

Relevant as of April 2021; sources in notes

SEARN

SEARN has four key objectives with the ultimate goal of supporting the attainment of universal health coverage within the region

Aims and background	Current environment	Trends
Date of initiation and rationale	• The South-East Asia Regulatory Network (SEARN) was launched in 2016 • Regulatory authorities in several countries in the region required support for enhancing technical capacity, staff and resources to perform effectively. Even well-resourced authorities have challenges in thorough evaluation of new products and enforcing existing regulations	*n/a*
Overall objectives and aspirations	• There are 4 key objectives 1) **Information sharing**: creating an enabling environment for information sharing on regulatory policies, guidelines, standards and outputs between NRAs 2) **Systems strengthening**: support regulatory capacity development and strengthening regulatory systems in the region 3) **Convergence**: promote alignment in approaches and requirements based on international standards and 4) **Collaboration**: develop work sharing and reliance processes to address common work areas • The initiatives would also accelerate progress towards achieving the Sustainable Development Goal 3 to ensure healthy lives and promote health and well-being for all through the attainment of universal health coverage [2]	*None identified to suggest changes in goal of enabling access to affordable medical products of assured quality, safety and efficacy*
Focus exclusively on vaccines vs all health technologies	• Specific working groups for medical products and medical devices/diagnostics, no distinction for vaccines [1]	*Working group 5 on medical devices and diagnostics was set up in 2018 to provide greater focus on this emerging area of importance*
Key stakeholders and donors	• WHO provided the initial secretariat with the intent that SEARN would become a self-sustaining inter-country network managed by the member states [3] • The Steering Group has 3 permanent members (India, Indonesia and Thailand) and two revolving members and 5 working groups 1) quality assurance and standards of medical products 2) good regulatory practices 3) vigilance for medical products 4) information sharing platform and 5) medical devices and diagnostics [3]	
Participating countries	• SEARN exists on a voluntary basis though all of the 11 Member States of WHO South-East Asia Region are involved. This includes Bangladesh, Bhutan, Democratic People's Republic Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand and Timor-Leste [3]	*No trends identified to suggest changes in membership*

Relevant as of April 2021; sources in notes

Activities are directed under the 5 working groups which cover the innovation pathway

Activities conducted		Description
Overarching regulatory focus areas		• Activities are determined by each of the 5 working groups and span the whole innovation pathway

1. **Facilitating research and development:** Clinical trial regulation, ethic review, scientific advice, supporting innovation etc.	✓	• WG1 focuses on quality assurance and standards of medical products. Activities include: [1]
		  • Map labs and capacities for testing medical products in SEAR countries
		  • Agree on priority list of medical products for mechanisms for testing
		  • Develop protocols, procedure and assessment scheme to establish inter-country/laboratory comparison amongst National Control Laboratories

2. **Evaluating applications for approval:** Recommendations for marketing authorisation, post-approval variations etc.	✓	• A pilot project for accelerated registration of fixed dose combinations is currently being run and feedback from the program will be discussed at the 2021 annual SEARN meeting • The project will organize a joint review assessment workshop for HIV or HCV products once a company simultaneously submits application in multiple countries (minimum 3) [2]

3. **Monitoring safety across the product lifecycle:** Overseeing pharmacovigilance, post-marketing surveillance etc.	✓	• WG3 focuses on vigilance for medical products. Activities include: [1]
		  • Engage in capacity building programs in vigilance
		  • Provide information to set up safety monitoring system for medical devices and IVD
		  • Develop SEARN vigilance newsletter
		  • Develop capacity for integrating pharmacovigilance with national health programs in SEARN member states

4. **Compliance and development of standards:** Quality and GMP guidelines, GCP/GDP inspections, batch inspections etc.	✓	• WG2 focuses on Good Regulatory Practices (GRP) including: [1]
		  • Self-assessment of the global benchmarking tool, develop common needs Institutional Development Plans and organize joint workshops for SEAR countries
		  • Make available a minimum set of information on GMP, good distribution practices, Good X Practice on NRA websites
		  • Map needs for capacity development and training needs with regional/global training opportunities

Relevant as of April 2021; sources in notes

The most notable achievement has been the development of an information sharing platform gateway available to local NRAs

Activities conducted	Description	
5. **Disseminating information:** International collaboration, HCP guidelines, patient information, industry engagement etc.	✓	• Annual meetings since 2017 with representation NRAs, WHO HQ, technical experts from Bill & Melinda Gates Foundation, Therapeutic Goods Administration Australia, Medicines Patent Pool Switzerland and Centre of Regulatory Excellence Singapore [1] • WG4 focuses on information sharing. Activities include facilitating conversations between NRAs and facilitate dissemination of information including best practices and alerts [2] • One of the notable progress from SEARN is the Information Sharing Platform Gateway which launched in 2018 at the 2nd World Conference on Access to Medical Products-Achieving the SDGs 2030' which consolidates all the publicly available information from the 11 drug regulators into one platform [3]
Key activities outside of the regulatory space (e.g. procurement)		• *Not included in SEARN scope of work*

Relevant as of April 2021; sources in notes

SEARN has showed early signs of sustainability, particularly in information sharing and harmonization of standards

Regulatory sustainability	Description
Fosters R&D and public health innovation	• *TBD – limited public information on this, to explore further in interviews*
Supports the local trade and manufacturing environment	• *Outside of SEARN's scope of work*
Supports information sharing and reliance between NRAs	• SEARN has established a Medicine Quality Control Laboratories network to identify sites with the capacity to provide testing support to SEA countries with limited strengths in this area [1]
Supports harmonization of standards	• There is an external Quality Assurance System including proficiency testing, rechecking, re-testing and onside evaluation of laboratories which allows member states to harmonise activities of the national control laboratories [1]
Embeds innovation and continuous improvement through regulatory science approaches	• The annual SEARN meetings involves technical presentations to share best practices from other initiatives. In the 2019 meeting this included the Triple-S project on Smart Safety Surveillance, Clinical Research and CEPI challenge models [1]
Has catalyzed any other initiatives	• *TBD – limited public information on this, to explore further in interviews*
Changing from a donor-funded project to a self-sustaining initiative	• WHO supports secretarial support though in 2018, SEARN identified that funding sources were required for other activities. Exploring sustainable funding models has been identified as an objective but limited information on progress [1]

Relevant as of April 2021; sources in notes

SEARN is at early stages of development with limited information on key performance metrics

Evidence of impact	Description
Number of assessments undertaken	*Although SEARN have hosted annual meetings in 2017, 2018 and 2019, the initiative is still at early stages of development. Any reference to progress relates to activities including the establishment of working groups for specific workstreams, regulator touchpoints between stakeholder groups, pilot projects for joint assessments etc. There is limited information on the assessment of SEARN against specific metrics or KPIs.*
Impact on time measurements (e.g. clinical trial approvals or vaccine registration)	
Uptake across participating countries and context-appropriateness of decisions at country level	
Uptake across participating countries	
Level of information sharing and transparency	
Changes in maturity of participating NRAs	
Notable vaccine examples	
Evidence of any other targets or KPIs being met	

Relevant as of April 2021; sources in notes

Understanding the key barriers will require further exploration in the expert interviews

Barriers to success	Description
Key challenges at initiative level	*There is limited information assessing the success and barriers of SEARN, to explore further in interviews*
Key challenges at country level	
External factors limiting progress and implementation	

Relevant as of April 2021; sources in notes

Secondary initiatives

CRS and AMA

Aims and background of multi-lateral initiatives

	CRS	AMA
Date of initiation and rationale	• Launched in 2016 to address inadequate legislation and resource constraints in regulation across the Caribbean Community and Common Market (CARICOM) [1]	• Not yet established – the AMA will enter into force 30 days after ratification of the treaty (established in 2019) by 15 AU member states, with 5 states completing this to date [4] • The AMA will build upon the foundations made by the AMRH to become the 2nd continental regulatory framework to enhance capacity of NRMAs and RECs to ensure timely and equitable access to high quality, safe and efficacious health technologies [4], [5]
Overall objectives and aspirations	• Through regional reliance mechanisms and capacity building, the CRS **aims to support member states to gain access to standardized quality assured medicines, reduce cost across the region and reduce workload/ resource use for NRAs** [1]	• **To co-ordinate, provide regulatory oversight and strengthen on-going regulatory systems** through harmonization of efforts within the AU's RECs, RHOs and member states and ensure cost-effective use of limited resources [6] • Efforts from the AMA aim to **compliment those of the NRAs, RECs and RHOs, who will still assess the majority of medical products** and have their own regulatory decision [6]
Focus exclusively on vaccines vs all health technologies	• Immediate focus is on the WHO list of essential medicines or products considered a priority for CARICOM member states by the CRS, which includes vaccines, test kits and biosimilars (plans to expand scope to medical devices) [2]	• Focus will encompass all health technologies, including vaccines (expedited focus for diseases that affect Africa disproportionately)
Key stakeholder and donors	• Managed under CARICOM's regional health body; the Caribbean Public Health Agency (CARPHA) [1] • Technical support gained from PAHO, and PAHO regulatory reference authorities (RRAs) • Donors include the BMGF, and the US FDA and Health Canada initially	• The AMA will be hosted by the member state elected by the Assembly of Heads of State and Government, and supported part time by NRA staff from AU member states • Donors are expected to be similar to those for the AMRH initative • Technical partners will include the WHO, the EMA and the FDA to achieve its mandate for reliance and participation on normative standards, technical cooperation and capacity building [6]
Participating countries	• CARICOM and CARPHA member states	• All interested AU members across the African Continent • 17 member states have signed the AMA treaty (but not yet ratified it)

Relevant as of April 2021; sources in notes

Focus areas across the regulatory lifecycle [1/2]

	CRS		AMA	
Overarching regulatory focus areas	• Supports regulatory capacity building and key regulatory functions by providing recommendations for MA, rational use and the quality and safety monitoring of medical products in the Caribbean [1]		• Harmonization and capacity strengthening efforts will cover all regulatory activities across the full product life cycle with clear roles and responsibilities at country, regional and continental level amongst regulators [5] • Building upon the work conducted by the AMRH with the AU Model Law, the AMA will aim to support overarching regulatory harmonization, promote cooperation and mutual recognition of regulatory decisions [5],[6] • AMA recommendations will act as a reference for AU member states to perform MA, joint assessments and GMP inspections, market surveillance, safety monitoring, oversight of clinical trials and coordination of quality control laboratory services	
1. Facilitating research and development	✘	• Out of scope (to verify in interviews)	✓	• Expected within the activities of the AMA to promote local pharmaceutical production, as stated within the AU Model Law
2. Evaluating applications for approval	✓	• Through reliance and information sharing with PAHO's regulatory authorities of reference (RRAs – such as the EMA or FDA for vaccines), the CRS carries out an accelerated/abridged review with a target time for scientific assessment of 90 days [1],[2] • Eligible products for the review include WHO/PAHO Strategic Fund essential medicines or products considered a public health need in CARICOM, WHO PQ reviewed products, RRA recommended products and WHO/RR EUL (for COVID-19 vaccines) [2] • Following a positive recommendation, member states are then responsible for issuing MA ideally within 60 days of communication from the CRS [2] • In 2018, the CRS evaluated 2 vaccines for cholera [1]	✓	• The AMA aims to accelerate and simplify access through transparent assessments based on common standards and predictable timely approvals instead of having individual requirements by NRAs [6] • The AMA proposes to convene pooled scientific expertise and capacities in joint assessments to enable expedited approvals that meet the required needs, particularly for conditions that affect Africa disproportionately [6]

Key: ✘ : Out of scope ~ : Not a key area of focus but some impact ✓ : Key areas of focus

Relevant as of April 2021; sources in notes

Focus areas across the regulatory lifecycle [2/2]

	CRS		AMA	
3. Monitoring safety across the product lifecycle	✓	• In tandem with the CARPHA Drug Testing Lab, the CRS maintains a voluntary network for regional pharmacovigilance (VigiCarib) for member states, industry and the public to electronically report drug related AEs and SF products, with incidents reported to WHO global databases if appropriate [1]	✓	• The AMA will ensure a concerted approach to reduce SF prevalence by coordinating market surveillance and information sharing among member states and RECs [6] • Additionally, AMA will complement efforts rom the Africa CDC by providing technical support in the quality control of drugs at the request of member states who do not have the capacity [4]
4. Compliance and development of standards	~	• Currently out of scope, however there are plans to expand to inspections of regional manufacturers in the future [1]	✓	• Compliance and development of standards will build off the efforts made within the AMRH and the agency will coordinate efforts for GMP inspections and related work sharing activities [4],[6]
5. Disseminating information	✓	• Encourages information sharing through MOUs with member states and has established a focal point network across member states [3] • CRS staff are mentored by RRA employees, supporting technical competency through the registration process, and plans to expand these training sessions to other functions [1],[2] • Recently, the CRS has agreed to share information (including non-public) on products recommended by the PAHO SF through a secure electronic platform (REPS-RISE), which is expected to support the CRS review process, enhance PAHO SF product surveillance and enhance regulatory strengthening in member states that are a part of CARPHA and utilize the PAHO SF [1]	✓	• The AMA plans to leverage the RCOREs developed by the AMRH to support training, information sharing and development of scientific guidelines for medicines and vaccines for priority diseases across Africa [4],[5]
Key activities outside of the regulatory space	• Engages with public procurement agencies to acknowledge CRS recommendations [3]		• *No information found – to be verified in interviews*	

Key: ✘ : Out of scope ~ : Not a key area of focus but some impact ✓ : Key areas of focus

Relevant as of April 2021; sources in notes

Secondary initiatives

African Regulatory Network (ARN)
Africa Regulatory Taskforce (ART)
European & Developing Country CT Partnership (EDCTP)

Aims and background of multi-lateral initiatives

	ARN	ART	EDCTP
Date of initiation and rationale	• The rationale for 'syncing' regulatory systems is due to the recognition that no single regulatory stakeholder can meet current regulatory challenges alone [1]	• ART was established during the COVID-19 pandemic to meet growing demands for COVID-19 vaccines in 2021 [1] • Expectations are that the demand will exceed global supply and so vaccines will likely be prioritized for countries who are 'ready' with an efficient regulatory environment and decision making process [1]	• EU-funded public-private partnership (with support from the European Union) launched in 2003 and renewed in 2014, with funding until 2024 • Formed to support collaborative research in order to develop accessible, suitable and affordable medical interventions for poverty-related infectious diseases in Sub-Saharan Africa (SSA)
Overall objectives and aspirations	• To encourage greater harmonization and convergence of regulatory requirements to ultimately enable faster and expanded availability of quality medical products [1] • ARN works with both NRAs and pharmaceutical industry to encourage greater harmonization of regulatory requirements	• The objective of ART was to provide support for an effective regulatory framework for COVID-19 vaccine in Africa [1]	• EDCTP's mission is to enhance research capacity and development of new or improved medical interventions for the identification, treatment and prevention of poverty-related infectious diseases in SSA through all phases of clinical trials • Objectives are to accelerate development of medical interventions, strengthen cooperation between EU and SSA, develop capacity for clinical research, and increase the impact and cost-effectiveness of EU research investments
Focus exclusively on vaccines	• No distinction across therapy areas, focus on all medical products	• Focus on COVID-19 vaccines [2]	• Scope includes all health technologies, with a particular focus on interventions which tackle poverty-related infectious diseases
Key stakeholder and donors	• ARN is an ad-hoc network of regulatory policy and technical standards committee of IFPMA [2]	• ART is a joint effort established by the Africa Centers for Disease Control and Prevention (Africa CDC), the African Union Development Agency (AUDA-NEPAD) and is coordinated by African Medicines Regulatory Harmonization (AMRH) and the WHO African Vaccine Regulatory Forum (AVAREF) [1]	• Unique governance structure which involves full and equal partnerships between all of the EU and SSA countries to create the General Assembly of the EDCTP Association • The African Union, European Union and the WHO also send representatives as observers to EDCTP General Assembly Meetings • Funded on a model of matched funding, where the European Union provides a certain amount based on matching contributions by EDCTP participating states
Participating countries		• Member States of African Union [1]	• Partnership between 14 EU and 16 SSA countries

Relevant as of April 2021; sources in notes

Note: since the research, ART has been incorporated into other bodies; there have been significant developments in EDCTP

Focus areas across the regulatory lifecycle [1/2]

	ARN		ART		EDCTP	
Overarching regulatory focus areas	• The overarching objective is support capacity building in Africa [1] • The approach is based on the concept of 6Cs which comes from convergence experience in Asia. It includes Cooperation, Collegiality, Capacity, Commitment, Communication and Convergence [1]		• Provide support for a regulatory framework for the COVID-19 vaccine in Africa [1]		• Key focus is to support and strengthen the research capacity, however the 2014-2024 strategic business plan focuses on strengthening regulatory frameworks in SSA countries to enable the research environment • Supports regulatory harmonization as a member of the AMRH and contributed to the formation of AVAREF through grants to the WHO global training programme for regulators [2], [3] • Outlines plans to strengthen national regulatory frameworks by collaboration with the WHO and the African Union	
1. Facilitating research and development	✓	• ARN supports national and regional bodies in product development review including clinical trials, manufacturing and control	✘	• Out of ART's scope of work	✓	• Issued a proposals to fund the establishment and capacity development of NRAs and national ethics committees to enable improved regulatory pathway activities directly related to clinical trials [1] • Funding has supported infrastructure development and human capital training for R&D and ethics reviews of CTs, and supported establishment of the Pan African Clinical Trials Registry • Acts as a partner to the Council on Health Research and Development (COHRED), which offers technical support on how to strengthen innovation systems and set priorities
2. Evaluating applications for approval	✓	• ARN supports regulatory pathway development assessment including support with pre-qualification [1]	✓	• ART developed a framework for market authorization of COVID-19 vaccines including 3 scenarios [1] 1. COVID-19 vaccines which received WHO Emergency Used Listing (EUL) or pre-qualification (PQ) approval 2. COVID-19 vaccines which have received approval from one or more stringent regulatory authorities (SRAs) but not yet through EUL/PQ 3. COVID-19 vaccines that have received neither of the above	✘	• *Currently out of scope – to be verified further in interviews*

Key: ✘ : Out of scope ~ : Not a key area of focus but some impact ✓ : Key areas of focus

Relevant as of April 2021; sources in notes

Note: since the research, ART has been incorporated into other bodies; there have been significant developments in EDCTP

Focus areas across the regulatory lifecycle [2/2]

	ARN		ART		EDCTP	
3. Monitoring safety across the product lifecycle	✓	• ARN supports post-marketing surveillance (pharmacovigilance and monitoring of quality issues) [1]	✘	• Out of ART's scope of work	✘	• *Currently out of scope – to be verified further in interviews*
4. Compliance and development of standards	✓	• One of ARN's key activities in norms and standard setting for national and regional medical product regulations [1]	✘		✘	
5. Disseminating information	✓	• ARN aims to facilitate ongoing development and resource sharing to enable stakeholder across the spectrum to contribute their own capacity, strength and expertise. Platforms for networking and information exchange identified as necessary support [1]	✘		✓	• Work conducted through the Council on Health Research for Development offers opportunities for constituencies to share best practices and new ideas [1] • Offers potential for pairing EU member states with participating African countries to act as a technical advisors and build regulatory capacity [1]
Key activities outside of the regulatory space	• Outside of ARN's scope		• Outside of ART's scope		• The key focus of the initiative is to fund clinical trials and research activities conducted by European-African consortia, support projects that strengthen the clinical research capacity and support fellowships that focus on the career development of individual researchers [2] • Additionally, EDCTP covers product-focused implementation research on delivery and uptake of medical research, and works towards strengthening dialogue between researches, communities and policy makers [2], [3]	

Key: ✘ : Out of scope ~ : Not a key area of focus but some impact ✓ : Key areas of focus

Relevant as of April 2021; sources in notes

Note: since the research, ART has been incorporated into other bodies; there have been significant developments in EDCTP

Appendix

Detailed assessment of the challenges identified across the regulatory lifecycle

Lifecycle challenges: Facilitating R&D of vaccines

Regulatory barrier	Implications on vaccine access and the vaccine innovation ecosystem in Africa	Impact assessment

Delay in clinical trial (CT) approvals	• **Fewer resources for rapid approval of multi-country, complex CTs** (compared to rest of world) means Africa is often too slow to participate in industry sponsored CTs. Similarly:
	  ○ Manufacturers organize competitive recruitment for global trials and slots are filled on first come first serve basis, slow trials application approvals in Africa means countries are often too late
	  ○ Lack of widespread awareness of AVAREF processes to support expedited CT approvals amongst some manufacturers
		●

	• **Limited funding and collaboration between regulators and Research & Development (R&D) teams** outside of pandemic and epidemic contexts to collaborate on clinical trial design and assess interim data. This can result in limited applicability of clinical data in global trials for local populations, as products are not being tested on specific gene types that are unique to the continent (e.g. HIV infection, HIV/TB co-infection) ○ Although collaborations have occurred in the case of pandemics, epidemics and for emergency research (e.g., Ebola, Yellow Fever, COVID-19), they do not happen in everyday practice	●
Limited digital capacity to support clinical trials oversight in Africa	• **Insufficient digital infrastructure to support oversight of global/industry sponsored CTs** (e.g. through automated processes or mobile applications), making **Africa a less attractive option for manufacturers to conduct trials in** ○ During the COVID-19 pandemic, clinical research has undergone a digital revolution to support consistent data collection, however not all countries and National Regulatory Authorities (NRAs) have been able to adapt, particularly in Africa	●
	• **Limited availability of guidelines to assess complex study designs** (e.g., human infection / challenge models), preventing progress in clinical trial research and impacting access to innovative product	●
	• **Inadequate digital capacity** prevents regulators from **gaining relevant experience** in reviewing complex trial designs	●
Nascent coordination between regulatory and ethics committees	• **Duplication of work and disagreements between National Ethics Committees (NECs) and NRAs** during CT protocol assessments and joint CT site assessments **can create a significant bottleneck to efficient approval** ○ There is 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	●
	• **Lack of technical and organizational capacity within ethics committees** to conduct efficient reviews or facilitate timely involvement in CTs	●

*Key: Impact on supporting innovation and enabling access to vaccines: **High**, **Medium**, Low*

Lifecycle challenges: Authorizing safe and effective vaccines

Regulatory barrier	Implications on vaccine access and the vaccine innovation ecosystem in Africa	Impact assessment
Relatively limited ability to conduct regulatory reviews for complex products outside of the WHO (PQ) scope	• **Deprioritisation of conducting regulatory reviews of products beyond priority public health focus** ○ Prior and current reliance on WHO PQ means countries are disincentivized from local capacity strengthening and are at risk of having significant regulatory gaps for localized epidemics which may lack prioritization globally	●
	• **Capacity gaps in the assessment of complex products**, such as monoclonal antibodies, biosimilars and biotechnology products for market approval	●
	• **Inexperience with vaccine related technologies and dossiers** has prevented National Regulatory Authorities (NRAs) to support or participate in reliance mechanisms due to lack of current trust in the decisions made by others	●
Strict international frameworks and centralized gatekeepers for vaccine approval	• Stringent **requirements of needing to operate at a maturity level 3** (according to the WHO Global Benchmarking Tool) to enable vaccine dossier approval prior to WHO approval **may enforce the requirements for NRAs to rely on WHO PQ** and Emergency Use Listings (EULs) procedures, even if there is local capacity to grant market approval ○ Despite having the capacity to review the COVID-19 vaccine dossier, NAFDAC (Nigeria's NRA) was not able to gain access to it until it was routed through the WHO, causing delays in the overall approval	●
	• **Significant approval delays create a huge disincentive for manufacturers to launch** when they have to interface with multiple countries and varying processes	●

	• **Low acceptance of unpublished or interim data from clinical trials** in non-pandemic context at the local NRA level (outside of the PQ/ GAVI process), unnecessarily slows down approvals for high unmet need areas preventing parallel manufacturing scale up
	  ○ During the Ebola outbreak, local countries lacked the legal framework or expertise to allow approval of vaccines with incomplete data despite the emergency needs
	  ○ For life-threatening diseases where the benefit is deemed to outweigh the risk, bodies such as the EMA and FDA allow for conditional and fast-tracked regulatory approval until additional data is gathered
		●

Lack of defined processes to support post-approval variations	• **Capacity gaps to review and approve post-approval product variations leading to vaccine stock-outs and shortages** ○ The timeline from WHO PQ approval to local approval can take years, often it would be 3-4 years after EMA approval when a vaccine is availably locally; by then there are often new variations to consider and could lead to local manufacturing plants becoming ineffective	●
	• **Inefficient post-approval changes are extremely time consuming for manufacturers,** which further disincentivizes launch and commercial viability	●

Key: Impact on supporting innovation and enabling access to vaccines: ***High****,* ***Medium****, Low*

Lifecycle challenges: Manufacturing and quality assurance

Regulatory barrier	Implications on vaccine access and the vaccine innovation ecosystem in Africa	Impact assessment
Nascent regulatory maturity and limited infrastructure to support the required oversight of emergent local vaccines manufacturers	• **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 ○ Although Bangladesh had the manufacturing capacity to export vaccines, GAVI were providing funding for self-procurement due to lack of a functional National Regulatory Authority (NRA) with sufficient WHO regulatory maturity	●
	• Though there is a clear political will to produce and manufacture vaccines, which has been exacerbated by the COVID pandemic, the **lack of NRAs operating at a maturity level 3 (ML3)** (based on the WHO Global Benchmarking Tool) **for producing vaccines across the continent prevents vaccine exportation**	●
Inconsistent capabilities in Good Manufacturing Practices (GMP) inspections	• Manufacturing facilities and operations that do not conform to good manufacturing practices certified by the WHO ultimately **limits scaling up quantities and achieving economies of scale that make local manufacturing more commercially viable** for routine vaccines	●
Insufficient legal powers to deter those engaged in support of sub-standard and falsified medicines	• **Lack of criminalization or enforcement of legal actions to disincentivize entry of sub-standard and falsified products,** resulting insecure supply chains • During the pandemic, falsified COVID-19 vaccines were administered to at least 800 people in Uganda; the vaccines were believed to be stolen from government bodies or manufactured locally without passing the necessary regulatory reviews	●

*Key: Impact on supporting innovation and enabling access to vaccines: **High**, **Medium**, Low*

Lifecycle challenges: Deploying vaccines within countries

Regulatory barrier	Implications on vaccine access and the vaccine innovation ecosystem in Africa	Impact assessment
Limited oversight of cold chain equipment and administration devices within WHO PQ	• **Underdeveloped infrastructure prevents expansion of national competencies required for vaccine delivery and access** (e.g., availability of cold-chain equipment) ○ Cold chain equipment and administration devices program is a critical aspect in WHO pre-qualification (PQ) but as it is chronically underfunded, widespread deployment of vaccines can be impacted	●

*Key: Impact on supporting innovation and enabling access to vaccines: **High**, **Medium**, Low*

Lifecycle challenges: Monitoring ongoing safety and effectiveness

Regulatory barrier	Implications on vaccine access and the vaccine innovation ecosystem in Africa	Impact assessment
Nascent digital infrastructure and resources for reporting adverse events information within a continental or national pharmacovigilance (PV) system	• **National pharmacovigilance capacities are undermined by the lack of digital infrastructure necessary for ongoing monitoring of vaccines** such as safety assurance and collection of Phase IV data. These gaps include lack of internet connectivity to support reporting via mobile applications and insufficient laboratory equipment for testing, resulting poor overall reporting rates within continental and national pharmacovigilance systems ○ Although the Seychelles had one of the highest roll outs of the COVID-19 vaccine, they have had the highest number of breakthrough infections, which have been a result of insufficient levels of pharmacovigilance and monitoring of vaccine effectiveness ○ NAFDAC (Nigeria's National Regulatory Authority) were able to utilize the GS-1 track and trace technology to reduce the occurrence of sub-standard and falsified products, however its widespread use across the country was limited by the lack of internet access to support the mobile applications ○ During the COVID-19 pandemic, Nigeria had insufficient laboratory equipment to test the Covishield vaccine being deployed	●
Limited capacity for some NRAs to conduct national PV activities (within a multi-country 3S framework)	• **A knowledge gap is created by the lack workforce expertise and relevant training,** preventing development and enhancement of safety monitoring, which limits both routine administration and effective pandemic preparedness • During the COVID-19 pandemic, although 3S was operationalized as a pilot programme, NAFDAC (Nigeria's National Regulatory Authority) experienced significant gaps in terms of work force capacity and training required for vaccine PV and safety monitoring, causing them to reallocate funds to sustain this as external funding was not sufficient ○ Due to limitations in the workforce, the Med Safety app could not be rolled out sufficiently in Nigeria	●
Limited ability for some NRAs to respond to issues identified and share the information effectively	• **Limited capacity to share issues raised** with other countries/ manufacturers **and effectively notify** health professionals/patient, resulting in poor response rates to adverse event (AE) issues and rapid withdrawal of products from markets	●

*Key: Impact on supporting innovation and enabling access to vaccines: **High**, **Medium**, Low*

Cross-cutting challenges: Financing (1/2)

Regulatory barrier	Implications on vaccine access and the vaccine innovation ecosystem in Africa	Impact assessment
Challenges with grant and funding management	• **These challenges disincentivize donors and other development partners to continue investment** due to the lack of impact predictability	●
	• **Unpredictable and consistent funding further limits opportunities for achieving self-sufficiency** when National Regulatory Authorities (NRAs) lack the autonomy to manage funds, preventing initiative/NRA progression ○ Development of the African Academy Science database Clinical Trials Community (CTC) registered the presence of ethics committees; was closed after the EDCTP funding ended due to inability to sustain further funding	●
	• **Slow absorption capacity across countries** (some NRAs still lack autonomy to manage budgets which are controlled centrally by the Ministry of Health (MoH)) prevent centralised financing at initiatives ○ AVAREF have not been able to achieve financial sustainability as fee structures vary across member states which means identifying a universal model at the continent level is challenging ○ Absorption capacity of regulatory guidance, WHO guidance and how to implement it is limited, which is particularly challenging in countries with a limited workforce capacity	●
Conflicting financing models dis-incentivize NRAs to harmonize	• **Fee models for the current processes**, such as Good Manufacturing Practices (GMP), dossier reviews and clinical trial protocol approvals, **disincentivizes governments to participate in harmonized processes** ○ Ethics committees and regulatory bodies are not financially incentivized to harmonize efforts as the bodies directly receive funds when conducting separate reviews while the distribution of funds in harmonized processes are not well defined	●
Limited industry incentive to participate when no clear impact on eventual access and uptake	• **Limited manufacturer participation in regional or continental initiatives** as that are either considered to be costly or time-consuming if there is no observable impact on eventual access and speed to market. This has further implications in limiting the possibility of user-fees to be established as a mechanism to support **self-sustaining initiatives**	●

*Key: Impact on supporting innovation and enabling access to vaccines: **High**, Medium, Low*

Cross-cutting challenges: Financing (2/2)

Regulatory barrier	Implications on vaccine access and the vaccine innovation ecosystem in Africa	Impact assessment
Different or changing priorities across donors	• **Lack of synergies between donors and initiatives supporting regulatory harmonization** has 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 needs	• **Inability for some countries to effectively participate in reliance activities due to their insufficient regulatory maturity or compete for grants due to weak proposals** • Countries with lower levels of regulatory maturity such as Burundi, South Sudan or Guinea Bissau have not been able to leverage existing regulatory programmes and have not had the opportunity to benefit from targeted capacity strengthening or political support for domestication of the African Union's (AU) Model Law	●
	• **No sustainable sources of finance for translation** which leads to ineffective use of resources to secure translation for every occasion it is needed	●
	• **Few resources to secure external partners to support proposal writing**	

*Key: Impact on supporting innovation and enabling access to vaccines: **High**, **Medium**, Low*

Cross-cutting challenges: Individual human resources

Regulatory barrier	Implications on vaccine access and the vaccine innovation ecosystem in Africa	Impact assessment
Varied technical skills and sometimes inexperienced workforce	• **Lack of ownership or accountability within NRAs to drive reliance activities and drive harmonization** ○ Although the AMRH has developed a monitoring and evaluation framework to support accountability amongst NRAs, reliance is not always built into NRA performance frameworks ○ Success of World Bank projects greatly improved once funding was provided directly to AMRH secretariats and steering committees, resulting in increased accountability vs channeling the funds via local governments	●
	• **Inconsistent training amongst member states of regional/continental initiatives,** causing discrepancies in their long-term aspirations as a group ○ The overall impact of AVAREF may be limited by the differences in the level of expertise of the regulators as AVAREF are not directly involved in the in-country training of inspectors (but is left to the discretion of each member state)	●

*Key: Impact on supporting innovation and enabling access to vaccines: **High**, **Medium**, Low*

Cross-cutting challenges: Institutional capacity

Regulatory barrier	Implications on vaccine access and the vaccine innovation ecosystem in Africa	Impact assessment
Lack of domestication of the AU Model Law and political prioritization of regulatory activities	• Lack of domestication of the African Union's (AU) Model Law hinders NRA autonomy, making **NRA activities susceptible to political instability and major shifts in the country**	●
	• Perceptions that regulation is not integral to the health system can result **in NRA recommendations being superseded by other parts of governments for national objectives**, driving national investment to other areas of healthcare • Regulatory is the often the last priority for governments; more immediate needs for improving public health such as hospital infrastructure are often addressed first ○ There are cases when the Minister of Finance has override NRA recommendations when there have been conflicting financial needs, risking the potential for substandard and falsified medical products to be circulated	●
	• **Politicization of NRAs prevents robust independent reviews of the dossiers** ○ Inspectors are unwilling to accelerate timelines even if processes can be made more efficient in fear of being regarded as not robust enough or fear of having to 'take the blame' when issues arise post approval	●
Limited professional recognition and workforce capacity with rapid staff turnover	• **Insufficient development or prioritization of project management skills to drive activities**, make decisions on the most appropriate use of resources and ensure that technical coordination is sustained	●
	• The lack of a sufficient human resources causes staff members to be overstretched, which may be temporarily **worsened through external partner involvement if they are removed from their day-to-day work** ○ In some African countries, a National Regulatory Authority (NRA) can be a team of one which oversees all regulatory activities	●
	• **Rapid turnover (to industry) due to low compensations and lack of clear career path** ○ This has been the case in countries like Nigeria, where the national FDA has lost its inspectors to the pharmaceutical industry once inspectors become more experienced	●
Uptake of emerging internal digital resources to support efficiencies	• **Limited internal digital resources to support daily activities required within NRAs and efficient use of resources**	●

*Key: Impact on supporting innovation and enabling access to vaccines: **High**, **Medium**, Low*

Cross-cutting challenges: Digital resources

Regulatory barrier	Implications on vaccine access and the vaccine innovation ecosystem in Africa	Impact assessment
Varied digital infrastructure to support effective convergence/ harmonization	• Gaps in digital infrastructure across the continent prevents efficient collaboration between countries and externally	●
	• Lack of interoperability between software/hardware across countries prevents efficient collaboration	●
	• Limited technology to support networking between local National Regulatory Authorities (NRAs) and international partners	●

*Key: Impact on supporting innovation and enabling access to vaccines: **High**, Medium, Low*

Cross-cutting challenges: Legal and policy environment

Regulatory barrier	Implications on vaccine access and the vaccine innovation ecosystem in Africa	Impact assessment
Inconsistent political willingness to participate in convergence/reliance due to the absence of trust and perceptions of loss of sovereignty	• **Some individuals within countries/ NRAs are averse to the concept of reliance** due to a misunderstanding of how the process works and wanting to protect their sovereignty	●
	• **Unwillingness to harmonize communications/process in a common language** ○ It is highly inefficient to translate materials as English is the working language within the regulatory space. It is extremely challenging to find regulatory expertise outside of English language (WHO was unable to find French experts from France, Canada or Switzerland)	●
	• **Limited guidance on clear actions to implement harmonized technical documents/recommendations** result in divergent practices across countries ○ Although 17 countries have adopted the AU Model Law, lack of specificity has prevented convergence of practices amongst NRAs as they have adopted the framework differently according to the local context/ priorities ○ Within the Pan-African Ethics Initiative, country ethics leaders were not able to come to concrete resolutions, preventing the initiative from gaining further funding by the EDCTP	●
Vaccine hesitancy	• **Few resources to build public confidence** on the regulatory approval of vaccines and limit the spread of vaccine misinformation to help facilitate access and uptake	●

*Key: Impact on supporting innovation and enabling access to vaccines: **High**, Medium, Low*

Appendix

Assessment of opportunities for regulatory strengthening

Based on the challenges identified, we have set out potential desired outcomes of what could be achieved from regulatory strengthening

Facilitating R&D of vaccines	Authorizing safe and effective vaccines	Manufacturing and quality assurance	Deploying vaccines within countries	Monitoring ongoing safety and effectiveness
• **Timely and consistent clinical trial (CT) approvals** which ensures agreed timelines are met across the continent • **Inter-operability and easy of information flow of clinical trial data** • **Scope potential for reviewing the way in which ethics are reviewed in relation to the clinical trials approvals process**	• **Seamless and timely review and authorisation** (for products outside of PQ scope for routine use) • **Seamless and timely registration of products** (emergency use) • **Fully harmonised process for post-approval changes**	• **Locally produced products by anchor states can be exported** due to their **ML3 status** and also meet global quality standards for local use, aligned with the WHO GBT and the competency framework • **Improved availability of safe, high quality and efficacious vaccines**	• **Effective immunization campaign with fit-for-purpose regulatory** oversight of downstream activities • **Effective supply chain oversight**	• **Effective continental monitoring of products and response to adverse events** • **Effective accountability for PV**

Notes: CT= clinical trial, PQ = WHO pre-qualification, ML3 = Maturity level 3 (as assessed by the WHO Global Benchmarking Tool), GBT = global benchmarking tool, PV = pharmacovigilance

There are cross-cutting enablers which are critical for achieving the desired outcomes in regulatory strengthening

Financing
• **Sustainable funding** for regulatory activities, continental reliance

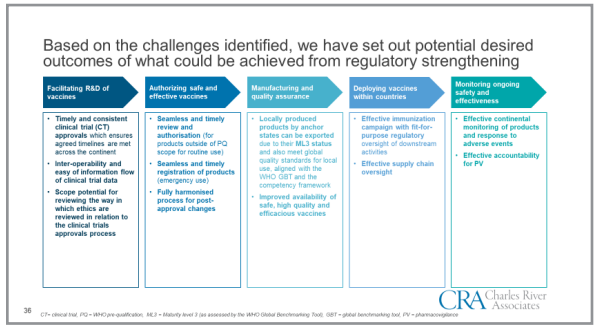
Individual human resourcing
• **Sufficient human capacity** to deliver effective vaccines regulatory oversight

Institutional capacity
• **Effective institutional capacity** to deliver national and continental regulatory priorities

Digital resources
• **Digital resources** are fit for purpose to support regulatory convergence and harmonization

Legal, Policy and Governance environment
• **Robust legal, policy and governance environment** which can support effective convergence and harmonization

Using the solutions as a foundation, we identified the required activities to achieve each desired outcome



Based on the identified solutions, specific activities were determined following a theory of change concept

Activities

Input

What is the investment?

For example:
- *Human resources*
- *Physical infrastructure*
- *Digital technology*

Output

What is the product of activities?

For example:
- *Strong political buy in*
- *Standardized and robust systems*

Outcomes

What is the desired change?

For example:
- *Functional systems*
- *Accountability and oversight on key metrics and KPIs*

KPIs = key performance indicators

Opportunities for investment can be grouped under three 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 +**

Solutions to **accelerate** developments in the regulatory environment (1/6)

Outcome	Key outputs	Activities	Timeframe	Relevant context
Timely and consistent CT approvals which ensures agreed timelines are met across the continent	Strengthened continental capacity to engage in regulatory sciences (workforce strengthening and support for AMA)	Participate in early engagement with AMA to support strengthened continental capacity to engage in regulatory science	Short / Medium / Long	●
		Streamlined ethics processes that are synchronized with CTA timelines	Short / Medium	●
Inter-operability and ease of information flow of CT data	Digital infrastructure to support clinical trials	Build digital infrastructure to support clinical trials	Short / Medium	●
Seamless and timely review and authorisation (for products outside of PQ scope for routine use)	AMA, RECs and ML3 NRAs can support regulatory decisions for all product types and clinical trial designs, including for more complex technologies such as monoclonal antibodies and products outside of WHO PQ scope	Build capacity (legal basis, skills, processes & linkages to NRAs) with AMA and other reliance pathways to support regulatory decisions for products outside of WHO PQ scope	Short / Medium / Long	●
	NRAs across the continent implement abridged reviews for all products approved by AMA/REC/ML3s, supported by suitable legal framework		Short/Medium	
	A standardized process for local NRAs to review complex technologies outside of PQ scope such that they approve products within agreed timelines		Short/Medium	

Relevant context: ● Epidemic ● Pandemic ● Routine ● Across all

Related positioning within regulatory lifecycle: Facilitating R&D of vaccines | Authorizing safe and effective vaccines | Manufacturing and quality assurance | Deploying vaccines within countries | Monitoring ongoing safety and effectiveness | **Critical enabler**

***Timeframe**: Short-term (within 5 years), medium-term (5-10 years), long-term (15+ years)*

CT = clinical trials, PQ = WHO pre-qualification, AMA = African Medicines Agency

Solutions to **accelerate** developments in the regulatory environment (2/6)

Outcome	Key outputs	Activities	Timeframe	Relevant context
Seamless and timely registration of products (emergency use)	Emergency guidelines are used and applied to enable registration within agreed timelines (support for AVAREF)	Support AVAREF member states to use and apply emergency guidelines to enable registration within agreed timelines	Medium	● ●
	Continental adaptation of policy framework to ensure regulatory support by ML3-5 regulators in emergency contexts	Scoping of the opportunities for adaptation of EY M4A type framework for African context	Short	●
		Scope potential adaptation of the existing framework for mature regulators provide support/authorization to countries requiring access to products for epidemic context	Short	●

Relevant context: ● Epidemic ● Pandemic ● Routine ● Across all

Related positioning within regulatory lifecycle: Facilitating R&D of vaccines | Authorizing safe and effective vaccines | Manufacturing and quality assurance | Deploying vaccines within countries | Monitoring ongoing safety and effectiveness | **Critical enabler**

***Timeframe**: Short-term (within 5 years), medium-term (5-10 years), long-term (15+ years)*

CT = clinical trials, PQ = WHO pre-qualification, AMA = African Medicines Agency

Solutions to **accelerate** developments in the regulatory environment (3/6)

Outcome	Key outputs	Activities	Timeframe	Relevant context
Fully harmonised process for post-approval changes	An effective end-to-end process converging across regulators which AMA oversees for timely post-approval changes to be applied at national level	Support AMA to oversee an effective end-to-end process converging across regulators for timely PAC to be applied at national level	Short/ Medium	●
Locally produced products by anchor states can be exported due to their ML3 status	Anchor states obtain ML3 status for vaccines	Build capacity in anchor states to obtain ML3 status for vaccines, in line with WHO GBT (and competency framework)	Short / Medium / Long	●
		Scope potential for development of centralized/hub-and-spoke laboratory network infrastructure to support local production (esp lot release)	Short/Medium/ Long	●
Improved availability of safe, high quality and efficacious vaccines	Legal enforcement measures are strengthened to prevent the product and supply of sub-standard and falsified medical products	Develop stronger legal enforcement measures to prevent the product and supply of SF products	Medium	●
	Penalties are developed with judiciaries	Develop penalties for SF products with judiciaries	Long	●

Relevant context:	● Epidemic ● Pandemic ● Routine ● Across all

Related positioning within regulatory lifecycle:	Facilitating R&D of vaccines	Authorizing safe and effective vaccines	Manufacturing and quality assurance	Deploying vaccines within countries	Monitoring ongoing safety and effectiveness	Critical enabler

***Timeframe**: Short-term (within 5 years), medium-term (5-10 years), long-term (15+ years)*

CT = clinical trials, PQ = WHO pre-qualification, AMA = African Medicines Agency

Solutions to **accelerate** developments in the regulatory environment (4/6)

Outcome	Key outputs	Activities	Timeframe	Relevant context
Effective supply chain oversight	AMA guidance for GDP is taken up by countries	N/A – covered under the benefits of supporting AMA	Medium	*N/A*
	Oversight of cold chain equipment under WHO PQ which is not currently funded	Support provision of cold chain oversight- funding, norms and standards (GDP and PQ)	Medium/Long	●
Sustainable funding for regulatory activities, continental reliance	An efficient fee-based system for AMA and related initiatives that operates sustainably with industry participation	Conduct a bottleneck/critical path analysis and support development of concrete plans for a user fee system for AMA, RECs and NRAs	Short/Medium	●
		Develop an effective, sustainable user fee system which incentivises industry (e.g. links to procurement decisions and offers concrete benefits to users in terms of speed to market and reduction of effort)	Medium / Long	●

Relevant context: ● Epidemic ● Pandemic ● Routine ● Across all

Related positioning within regulatory lifecycle: Facilitating R&D of vaccines | Authorizing safe and effective vaccines | Manufacturing and quality assurance | Deploying vaccines within countries | Monitoring ongoing safety and effectiveness | **Critical enabler**

***Timeframe**: Short-term (within 5 years), medium-term (5-10 years), long-term (15+ years)*

CT = clinical trials, PQ = WHO pre-qualification, AMA = African Medicines Agency

Solutions to **accelerate** developments in the regulatory environment (5/6)

Outcome	Key outputs	Activities	Timeframe	Relevant context
Effective institutional capacity to deliver national and continental regulatory priorities	Workforce is strengthened and staff turnover is reduced	Build capacity and retention in regulatory workforce (fellowships, training through others)	Short/Medium/Long	●
		Build capacity and retention in regulatory workforce (using domestication of AU Model Law linked to continental curriculum, better salary etc)		●
		Build capacity regulatory workforce (strategic review, funding and expansion of RCOREs)		●
Digital resources are fit for purpose to support regulatory convergence and harmonization	Regulatory activities across the continent are harmonised employing advanced digital tools which are future proofed (potentially including technologies such as blockchain, WISER and other data management systems to support convergence)	Scoping study to investigate the feasibility of implementation of advanced digital tools	Long	●
Sufficient human capacity to deliver effective vaccines regulatory oversight	NRA workforce is developed in alignment with WHO competency framework/best practices in ML4/5 agencies	Policy engagement and review of regulatory pathways in FDA/EMA	Medium	●

Relevant context: ● Epidemic ● Pandemic ● Routine ● Across all

Related positioning within regulatory lifecycle: Facilitating R&D of vaccines | Authorizing safe and effective vaccines | Manufacturing and quality assurance | Deploying vaccines within countries | Monitoring ongoing safety and effectiveness | **Critical enabler**

***Timeframe**: Short-term (within 5 years), medium-term (5-10 years), long-term (15+ years)*

CT = clinical trials, PQ = WHO pre-qualification, AMA = African Medicines Agency

Solutions to **accelerate** developments in the regulatory environment (6/6)

Outcome	Key outputs	Activities	Timeframe	Relevant context
Robust legal, policy and governance environment which can support effective convergence and harmonization	Political leaders actively advocate for reliance and recognise the role of regulators the importance of the health system; National Medicines Policies and Pharmacy departments openly recognise reliance and promote its uptake	Ongoing political and policy engagement to promote understanding of reliance benefits	Medium	●
	Standardized, synchronized approaches for ethics review and clinical trials approvals	Scoping study & engagement activity on the potential for creating a continental approach for ethics review aligned with AU Model Law, which sets out standardized approaches for integrating ethics review and clinical trials approval	Short / Medium / Long	●
	Domestication of AU Model law to ensure effective implementation	Support to CSOs with regional and country presence to promote domestication of AU Model Law	Short / Medium	●
	Strengthened continental and national pathways to support NRAs to benefit from ML5 recommendations, including for emergency use authorisations	Scoping of the application of the EU M4A/Article 58 procedure	Short / Medium	●
Sustainable funding for regulatory activities, continental reliance	Efficient and coordinated international funding to ensure effective resource allocation in areas of greatest need	Support a coordinated funders platform to prioritise resource allocation (esp. for cross-cutting support for CIP/AMRH PP)	Short/Medium	●
	AMA is established and implemented with appropriate policies and governance	Seed funding for creation of AMA PMO & specific scoping studies for evidence-informed decision making by AMA Secretariat & leadership	Short/Medium	●

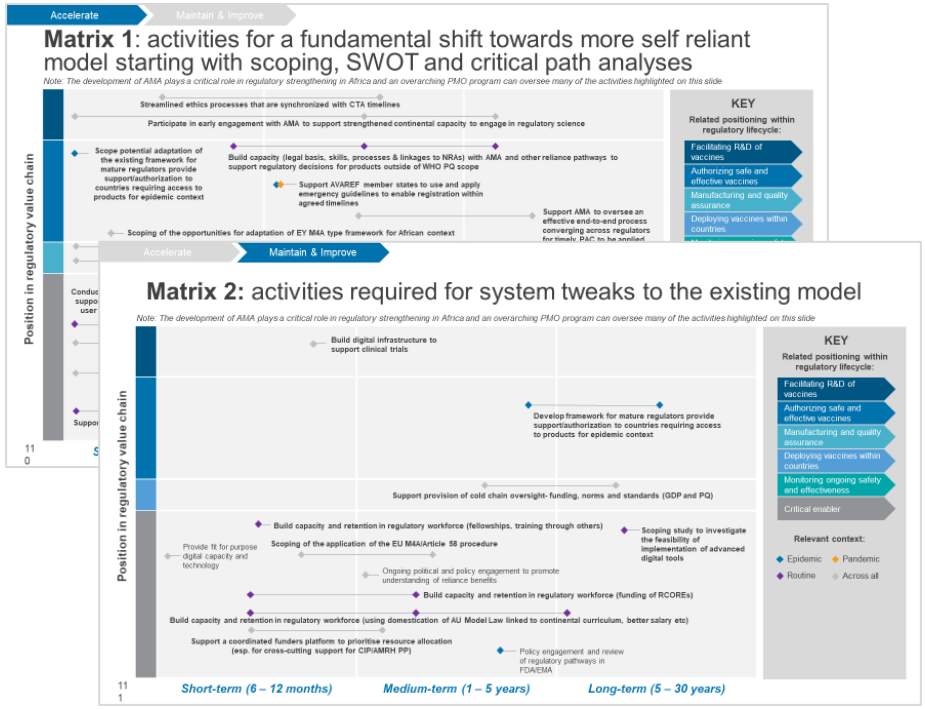
Relevant context:	● Epidemic ● Pandemic ● Routine ● Across all

Related positioning within regulatory lifecycle:	Facilitating R&D of vaccines	Authorizing safe and effective vaccines	Manufacturing and quality assurance	Deploying vaccines within countries	Monitoring ongoing safety and effectiveness	Critical enabler

***Timeframe**: Short-term (within 5 years), medium-term (5-10 years), long-term (15+ years)*

CT = clinical trials, PQ = WHO pre-qualification, AMA = African Medicines Agency

We have mapped relevant actions into two packages 1) accelerate and 2) maintain and improve objectives



1 Accelerate

Shift away from dependance on global partners towards greater self-reliance

2 Maintain and improve

Dramatic improvements to the current donor-driven model

Example activities

Matrix 1: activities for a fundamental shift towards more self reliant model starting with scoping, SWOT and critical path analyses

Note: The development of AMA plays a critical role in regulatory strengthening in Africa and an overarching PMO program can oversee many of the activities highlighted on this slide

Position in regulatory value chain

- Streamlined ethics processes that are synchronized with CTA timelines
- Participate in early engagement with AMA to support strengthened continental capacity to engage in regulatory science
- Scope potential adaptation of the existing framework for mature regulators provide support/authorization to countries requiring access to products for epidemic context
- Build capacity (legal basis, skills, processes & linkages to NRAs) with AMA and other reliance pathways to support regulatory decisions for products outside of WHO PQ scope
- Support AVAREF member states to use and apply emergency guidelines to enable registration within agreed timelines
- Support AMA to oversee an effective end-to-end process converging across regulators for timely PAC to be applied at national level
- Scoping of the opportunities for adaptation of EY M4A type framework for African context
- Scope potential for development of centralized laboratory network infrastructure
- Build capacity in anchor states to obtain ML3 status for vaccines, in line with the WHO GBT and competency framework
- Conduct a bottleneck/critical path analysis and support development of concrete plans for a user fee system for AMA, RECs and NRAs
- Develop penalties for SF products with judiciaries
- Develop stronger legal enforcement measures to prevent the product and supply of SF products
- Develop an effective, sustainable user fee system which incentivises industry (e.g. links to procurement decisions and offers concrete benefits to users in terms of speed to market and reduction of effort)
- Seed funding for creation of the AMA PMO and specific scoping studies which support evidence-informed decision making by the AMA Secretariat and leadership
- Scoping study and engagement activity to support inclusion of ethics review into continental Model Law which sets out standardized approaches for integrating ethics review and regulatory approval
- Support to CSOs with regional and country presence to promote domestication of AU Model Law

KEY

Related positioning within regulatory lifecycle:

- Facilitating R&D of vaccines
- Authorizing safe and effective vaccines
- Manufacturing and quality assurance
- Deploying vaccines within countries
- Monitoring ongoing safety and effectiveness
- Critical enabler

Relevant context:

- Epidemic
- Pandemic
- Routine
- Across all

Short-term (6-12 months) ***Medium-term (1 – 5 years)*** ***Long-term (5 – 30 years)***

Matrix 2: activities required for system tweaks to the existing model

Note: The development of AMA plays a critical role in regulatory strengthening in Africa and an overarching PMO program can oversee many of the activities highlighted on this slide