Vaccine Equity for Africa

Technology Transfer and Establishment of Sustainable Vaccine Production in Africa-

A Regulatory Perspective

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List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AEFI	Adverse Events Following Immunisation
AIFA	Agenzia Italiana del Farmaco
AMA	African Medicines Agency
AMRHI	African Medicines Regulatory Harmonisation Initiative
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé
ASEAN	Association of South East Asian Nations
ATMP	Advanced Therapy Medicinal Product
AU	African Union
AUDA-NEPAD	African Union Development Agency New Partnership for Africa´s Development
AVAREF	African Vaccine Regulatory Forum
BDS	Bulk Drug Substance
BEVS	Baculovirus Expression Vector System
BoDs	Board of Directors
CDC	Centres for Disease Control and Prevention
CMC	Chemistry Manufacture Control
COVAX	COVID-19 Vaccines Global Access
CRP	Collaborative Registration Procedure
CTD	Common Technical Document
CTL	Cytotoxic T Lymphocyte
DP	Drug Product
DS	Drug Substance
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
EAC	East Africa Community
EAEU	Eurasian Economic Union
EC	European Commission
EMA	European Medicines Agency
EU	European Union
EUL	Emergency Use Listing
FAMPH	Federal Agency for Medicines and Health Products
FDA	Food and Drugs Authority
FDAR	Food and Drugs Assessment and Registration
FDISM	Food and Drugs Inspection and Safety Monitoring
GBT	Global Benchmarking Tool
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
IDP	Institutional Development Plan
IPD	Institute Pasteur Dakar
IVD	In Vitro Diagnostic
IVT	In Vitro Transcription
LMI	Low- and Middle-Income Country
LNP	Lipid Nanoparticle
MA	Marketing Authorisation

MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board
MHRA	The Medicines and Healthcare Products Regulatory Agency
ML1	Maturity Level 1
ML3	Maturity Level 3
MoH	Ministry of Health
NCL	National Control Laboratory
NRA	National Regulatory Authority
NTP	Nucleoside Triphosphate
PACTR	Pan-African Clinical Trials Registry
PAHO	Pan American Health Organization
PAVM	Partnerships for African Vaccine Manufacturing
PCR	Polymerase Chain Reaction
PEG	Product Evaluation Group
PEI	Paul Ehrlich Institute
PHEIC	Public Health Emergencies of International Concern
PIL	Patient Information Leaflet
PMPA	Pharmaceutical Manufacturing Plan for Africa
PQ	Prequalification
PQP	Prequalification of Medicines Programme
PQVAR	Prequalification Annual Report
PV	Pharmacovigilance
QA	Quality Assurance
QC	Quality Control
QMS	Quality Management System
RCN	Regulatory Convergence and Network
RRS	Regional Regulatory System
SEC	Size-exclusion Chromatography
SII	Serum Institute of India
SIV	Simian Immunodeficiency Virus
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SP	Strategic Plan
TB	Tuberculosis
TGA	Therapeutic Goods Administration
TMDA	Tanzania Medicines and Medical Devices Authority
UFDF	Ultrafiltration/Diafiltration
UN	United Nation
UNICEF	United Nation Children´s Fund
VPQD	Vaccine Prequalification Dossier
VVM	Vaccine Vial Monitor
WCB	Working Cell Bank
WHO	World Health Organization
WHOPAR	WHO Public Assessment Report
WHOPIR	WHO Public Inspection Report
WLA	WHO-listed Authority

1. Executive summary

The COVID-19 pandemic has exposed the dependency of many countries, especially in the Global South, on a small number of vaccine-producing countries. Following the realisation, the World Health Organization (WHO) adopted a resolution "Strengthening local production of medicines and other health technologies to improve access" in May 2021, focussing on local manufacturing of vaccines. In parallel, several tech transfer hubs were initiated on the African continent.

Following the summit on vaccine manufacturing organised by the African Union (AU), the Africa CDC has launched the Partnerships for African Vaccine Manufacturing (PAVM) Task Force with a clear mandate, operating model, and governance structure to enable sustainable African vaccine manufacturing.

Embodied in the effort to establish sustainable vaccine manufacturing in Africa is the preparation of a White Book to evaluate the challenges and tools necessary to achieve the goal of sustainable vaccine manufacturing in Africa, by Africa and for Africa. The main focus of the White Book aims at introducing the concept of combined technical and regulatory transfer of fully functional vaccine manufacturing units and ensuring a broad understanding on the following aspects:

1. **Short-term goal: functional and sustainable production of SARS-CoV-2 vaccine in Africa within 2 years**

The principal idea behind the technical and regulatory transfer approach (also referred to as tech and reg transfer) takes advantage from the close and long-lasting liaison between the European Medicines Agency (EMA), national regulatory agencies of the European Union (EU) Member States and the WHO in terms of establishing and commonly agreeing on licensing procedures.

In principle, any vaccine regulated by EMA and licensed by the European Commission (EC) is eligible for prequalification by WHO. The WHO Prequalification is based on the licensure of recognised national regulatory authorities (NRAs), among them EMA. Prequalification by WHO allows purchase of these vaccines by countries or organisations. As all SARS-CoV-2 vaccines licensed in the EU are listed for emergency use, the manufacturing process behind is, in principle, also covered by that scheme.

As such, transfer of an exact copy of a vaccine manufacturing facility as licensed in the EU to Africa for local manufacturing and procurement would, in principle, be equivalent to distributing a prequalified vaccine produced in the EU. Consequently, reliance on a technology already approved and licensed in the EU is proposed as an interim solution enabling fast set up of urgently needed SARS-CoV-2 vaccine manufacturing on the African continent.

This White Book elaborates in detail how such local manufacture could be achieved, in accordance with an already existing regulatory framework.

2. **Long-term goal: creating a regulatory framework that would allow independent and self-sustained, high-quality regulatory assessment of vaccine manufacturing in Africa**

In addition to the tech transfer, utilisation of the WHO Emergency Use and Listing procedure and reliance on EU licensures that will enable fast initiation of approved SARS-CoV-2 vaccine production in Africa, an alternative and more sustainable approach should be developed **in parallel**.

In this White Book we briefly outline how such self-sustainability could be achieved by considering the currently existing regulatory environment in Africa, the initiatives proposed by African States, the AU, the PAVM Task Force, and WHO, as well as the current political and socio-economic landscape.

It is important to highlight that long-term sustainability of vaccine manufacturing in Africa will depend on the existence of highly efficient, mature regulatory systems to enable regulatory oversight of vaccine manufacture.

The export of vaccines manufactured locally is only possible once the product manufactured locally is prequalified by WHO. To achieve this, the country of manufacture must reach Maturity Level 3 (ML3) for vaccines in accordance with WHO's classification system – the Global Benchmarking Tool (GBT) (WHO).

To achieve this important goal, initiatives like the one described in this White Book could become very beneficial. In principle, the growing manufacturing experience and regulatory expertise on the African continent will be gathered alongside production of mRNA, recombinant protein, and other vaccines. These experiences and infrastructure should be then utilised in parallel to help creating a long-lasting and self-sustainable production in African countries of urgently needed vaccines.

2. Introduction

The ongoing SARS-CoV-2 pandemic has again demonstrated that although development and licensure of safe and effective vaccines is possible within unprecedented short timelines, availability and procurement is imbalanced alongside a gradient ranging from the very rich to the very poor countries. This imbalance is particularly visible in countries and regions that do not have own vaccine production facilities, or in case they do have, the available facilities are unsuitable for high end vaccine production based on novel technologies and manufacturing processes.

Africa is particularly affected as basically no infrastructure for sustainable state of the art vaccine production is available. In addition, regulatory systems and agencies are mostly immature to efficiently handle licensure and control of vaccines and manufacturing facilities. Some African countries, such as Ghana and Tanzania, are successfully building up regulatory infrastructures, aimed at facilitating the establishment and control of vaccine production. In addition, South Africa has the National Control Laboratory (NCL), the only one recognised by WHO in Africa. However, those countries will still be dependent on technology transfers from industrialised countries for the near future.

The concept presented in this White Book proposes a novel pathway aimed at making Africa more independent from vaccine-producing and exporting countries. The concept implies fully functional vaccine production units transferred to interested African countries. Vaccines produced in these units are licensed in the country or region of origin (primarily the EU) and are either prequalified or listed for Emergency Use by WHO. This combined transfer of technical and regulatory components should allow for an immediate onset of production of mRNA, recombinant protein-based and/or other SARS-CoV-2 vaccines, following successful technical and regulatory transfer.

The concept allocates clear roles to the manufacturer of the licensed vaccine, WHO, local ministries as well as competent authorities in selected African countries based on a mutual and pre-defined agreement. Successful translation into practice of the proposed concept relies on the acceptance of allocated roles and fulfilment of obligations linked to these roles as described in chapters 9, 11, 12, and 13 of the White Book. Most notably, the entire concept takes advantage from scientific and regulatory principles agreed on globally at the level of the WHO.

There is no intent to interfere with national or regional governmental or political structures. The concept is exclusively focused on the rapid set up of a fully functional and licensed production of SARS-CoV-2 vaccines in a first step and the development, licensure, and production of novel vaccines on a long-term basis.

Accordingly, following successful execution of the first step the same manufacturing units can be used to produce other vaccines most urgently needed in Africa to protect the African population from endemic infectious diseases. This second as well as any further steps are not described in the White Book as issues pertinent to the development and licensure of novel vaccines against endemic infectious disease are much more complicated compared to the technical and regulatory transfer of fully functional and licensed SARS-CoV-2 vaccine production units.

The principal aim of the White Book is to present background information on scientific and regulatory principles applied worldwide for vaccine licensure, production, and procurement.

3. Scope

The White Book is focused on the technical and regulatory transfer (also referred to as tech and reg transfer) and the implementation in selected African countries of fully functional SARS-CoV-2 vaccine production units. The term “fully functional” refers to either Drug Product (DP) production ready for fill and finish, or Bulk Drug Substance (BDS) to be further processed into filled and finished vaccines. Depending on the vaccine manufacturing process, tech transfer of DP fill and finish would be a simpler process, as compared to manufacture of BDS.

A number of African countries are partnering with established vaccine producers for tech and reg transfer along the lines discussed here.

The roles of individual partners, such as the manufacturer and Marketing Authorisation Holder (MAH) of the individual SARS-CoV-2 vaccines, EMA and national regulatory agencies of EU Member States, WHO, national ministries and NRAs in African countries will further be defined and described in detail following mutual agreement on the concept laid down in the White Book.

4. The evolution of drug regulation – from divergent to convergent regulatory systems

The necessity of establishing rules for the manufacture and distribution of drugs was recognised more than 100 years ago. These initiatives emerged from accidents and crises resulting from the manufacture and use of unsafe and/or ineffective products. Consequently, food and drug laws were introduced by individual countries, complemented by more specific guidelines regulating product or product class specific aspects. Although rules and procedures had the same objectives, namely standardising manufacture and control of products, some regulatory aspects were interpreted differently by countries or regions making it difficult for manufacturers to follow divergent guidance for one and the same product. This dilemma triggered a paradigm shift in drug regulation in favour of harmonised rather than individualised guidance and regulation.

The EU was frontrunning in that respect by initiating already in the 1960s (Legal framework of medicinal products in the EU) a system of harmonised rules and procedures applicable in all Member States. This initiative resulted in the foundation of EMA in 1995 (History of EMA) and from thereon in the development of regulatory principles applying to all medicinal products licensed in the EU (see chapter on rules governing medicinal products in Europe). Other regions as for example Latin America were following that path with the same success (Pan American Network for Drug Regulatory Harmonization).

In order to strengthen the regulatory capacity for oversight of medical products globally, WHO encourages international cooperation among regulatory authorities in all its forms, including convergence, harmonisation, information- and work-sharing, reliance, and recognition (Global and Regional Regulatory Harmonization Initiatives, Harmonisation for Better Health).

The Regulatory Convergence and Network (RCN) Team supports Member States in all activities related to regulatory convergence, regional or international regulatory networks and harmonisation initiatives.

Accordingly, harmonisation of requirements, i.e., legislations, scientific and regulatory guidelines, procedures, etc., is a basis for successful collaboration in medicines regulation. While implementing medicines regulations, it should be noted that this will only be effective if all major aspects of regulation are addressed. If successful, harmonisation of technical requirements for the development, licensure and control of medicinal products is a major advantage for all stakeholders for numerous reasons:

- Pharmaceutical companies must generate only one data set for all regions, and consequently the Chemistry Manufacture Control (CMC) development as well as the number and extent of nonclinical and clinical investigations is harmonised.
- The cost of development of regulatory documentation both for new drugs and multisource/generic medicines is reduced, which can lead to lower prices.
- Common regulatory standards for scientific evaluation and inspection facilitate regulatory communication and information sharing.
- Local products are more likely to be acceptable for export to other countries.

- Faster access to medicines of high public health value (paediatric medicines, medicines for major diseases or for emergencies in national settings etc.).
- Increased competitiveness resulting from newly developed common markets.

Promoting medicines regulatory cooperation and harmonisation in Africa

The African Medicines Regulatory Harmonisation Initiative (AMRHI) was established in 2009 with the intention to improve health in the African Region by increasing access to safe and effective medicines of good quality. This can be accomplished by strengthening the technical and administrative capacity of participating national medicines regulatory authorities. AMRHI restricts its focus to medicines registration and specifically to the registration of priority essential medicines (mostly generic pharmaceuticals) to maximise near-term patient benefit and impact the critical disease burden facing Africa.

Nevertheless, soon after the COVID-19 pandemic has stricken Africa, it became obvious that more intracontinental initiatives and urgent actions are needed to enable establishment of local vaccine manufacture facilities, and to strengthening the regulatory oversight in the continent. As such, WHO adopted a resolution "Strengthening local production of medicines and other health technologies to improve access" in May 2021, focussing on local manufacturing of vaccines. In parallel, several tech transfer hubs were initiated on the African continent.

Following the summit on vaccine manufacturing organised by the AU, the Africa CDC has launched the PAVM Task Force with a clear mandate, operating model, and governance structure to enable sustainable African vaccine manufacturing.

As of November 5th, 2021, the Treaty for the Establishment of the AMA entered into force. The AMA shall build on the efforts of the AMRHI to facilitate harmonisation of regulatory requirements and practice among the NRAs of the AU Member States (Union, 2021).

These collaborative mechanisms for medicines regulatory systems and processes at the regional/sub-regional levels should translate into improved regulatory approval processes and operational efficiencies at the national level. In this regard, the project aims to increase the capacity of national medicines regulatory authorities and specifically strengthen the administrative, structural, and technical elements of medicines regulation. Example of the regulatory capacity building is the Collaborative Registration Procedure (CRP) for WHO-prequalified products, which accelerates registration through improved information sharing between the WHO Prequalification of Medicines Programme (PQP) and NRAs (WHO Prequalification of Medicines Programme). In doing so, the project will help countries to enhance and facilitate their decision-making processes regarding the registration of medicines, as well as exercise more control over medicines circulating on the market. Regulatory capacity building and facilitation of information exchange are thus indispensable components of the project.

Specifically, the project objectives include:

- To create a collaborative network through partnership between medicines regulatory authorities of participating countries and/or selected sub-regional economic blocks.
- To harmonise technical requirements for the regulation of medical products and build confidence so that agreed harmonised standards are implemented and respected by participating authorities.

- To establish a framework for joint evaluations of application dossiers and inspections of medicine manufacturing sites resulting in mutual recognition.
- To strengthen the capacity for regulatory oversight.

Within the framework of the AMRHI, the WHO Medicines Regulatory Support Programme has organised and technically supported several regional preparatory activities in initiating harmonisation.

These and other harmonisation initiatives led by WHO are very helpful as they provide the basis for the straightforward and successful implementation of the tech and reg transfer concept proposed in this White Book.

5. Regulatory science as a new discipline accelerating vaccine development and licensure

Regulatory science is the foundation of regulatory decision-making and is used to assess the quality, safety, and efficacy of human medicinal products throughout their lifespan. The domains, covered by regulatory science, are considered to include both basic and applied biomedical sciences (such as microbiology, genetics, pharmacology, and biostatistics), clinical trial methodology and epidemiology, and social sciences (such as decision sciences, risk assessment, and communication). Regulatory science aims to contribute to the development of new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of regulated products (Elmgren et al., 2013).

However, for many innovative areas such as Advanced Therapy Medicinal Products (ATMPs), novel concepts to respond to emergency or outbreak scenarios or adaptive pathways to licensure, significantly contributing to the abbreviation of development and review timelines, regulators worldwide have not yet developed adequate principles to further establish a global regulatory science agenda. The aim of such agenda is to transform individual efforts into a coordinated action plan to support global licensure goals. Ultimately, advances in regulatory science will contribute to improved and faster access to innovative medicinal products.

Development of product or product class specific regulatory agendas provides a catalyst and unique opportunity for regulators worldwide to develop and propose a global regulatory science agenda for innovative medicinal products. Regulatory oversight is critical to allow access to these products that are safe, effective, and of assured quality. Methods, used by regulators, need to constantly evolve so that scientific and technological advances are applied to address novel challenges, and to provide an increased understanding of benefits and risks of existing products. Regulatory science builds on high-quality basic research and encompasses at least two broad categories. First, there is laboratory-based regulatory science. Illustrative examples include development of correlates of efficacy; or correlates of safety; or of improved product characterisation and potency assays. Included in such science would be tools to standardise assays used for regulatory purposes. Second, there is a science to develop regulatory processes. Illustrative examples include adaptive clinical trial designs; or tools to analyse the benefit-risk decision-making process of regulators; or novel pharmacovigilance methodologies. Included in such science would be initiatives to standardise regulatory processes (e.g., definitions of terms for adverse events [AEs] following use of individual products).

The aim of a global regulatory science agenda is to transform current national or regional efforts, mainly by experienced regulatory agencies specialised on the regulation of novel products or product classes, into a coordinated action plan to support global development programs.

The concept of tech and reg transfer proposed in the White Book is a direct result of continuous and successful efforts to set in force and constantly improve a globally agreed regulatory science agenda.

6. The complexity of medicinal products – from small molecules to complex vaccines

Traditionally, the treatment of human disease has been dominated by small molecule drugs. Small molecules are used to treat a variety of diseases and conditions and can be quite diverse in their mechanisms of action. Because of their small size and typical physiochemical properties, small molecules can be effective enzyme inhibitors and allosteric modifiers and can target extracellular proteins or intracellular receptors in the cytosol, nuclei, and central nervous system. Despite their perceived limitations, and with a recent resurgence, small molecules remain the major component of an ever-expanding therapeutic toolbox.

However, about 35 years ago, advances in biotechnology enabled the synthesis of certain biological molecules (primarily proteins) in microorganisms and other living cells using recombinant DNA technology. From these early discoveries and subsequent innovations, the realm of biologics has expanded to include a wide range of products. In addition to therapeutic proteins and antibodies, biologics also include:

- ATMPs including Cell, Gene Therapy and Genome Editing Products.
- Recombinant blood products.
- Vaccines and virus-based products used as gene transfer vectors, oncolytic and immunovirotherapeutic agents.

It goes without saying that the structure of biological medicinal products, or biologics, is much more complex compared to small molecule-based medicinal products. This has important implications as regards the manufacturing and control strategy as the primary, secondary and tertiary structures of protein-based medicinal products cannot be characterised at the level of the finished product. While small molecule-based medicinal products can sufficiently and reliably be characterised by appropriate physico-chemical methods at whichever production stage, most biologics cannot, as efficient methods detecting changes to the original structure proven to be safe and effective are often not available. If available, the impact of detectable changes on safety and efficacy is often difficult to evaluate.

Amongst all biologics, vaccines belong to the most complex class of products as they are composed of whole virion or microbial organisms (live attenuated or inactivated), live viral vectors, Lipid Nanoparticle (LNP)-packaged mRNA, antigen components extracted from wildtype pathogens or recombinant proteins produced in various expression systems. As such, vaccines require a scientific and regulatory concept that differs in many aspects from other biologics.

Moreover, unlike other medicinal products vaccines are given to a largely healthy population from birth onwards requiring adherence to the highest possible manufacturing standards to reduce reactogenicity and to ensure long-term safety as well as efficacy and effectiveness.

Lastly, vaccines belong to the most widely used and most effective medicinal products saving millions of lives every year. The principle of vaccination is applied since more than 200 years and since then standards established for manufacturing and control, nonclinical and clinical testing have been steadily refined resulting in excellent safety and effectiveness records of all licensed vaccines currently being on the market. Nowadays, these standards are acknowledged worldwide helping to

further increase the trust in vaccines and vaccination programs despite the devastating activities of anti-vaccine campaigners.

This enormous wealth of knowledge and experience in combination with a well-established and globally accepted regulatory framework creates the basis for pandemic preparedness and early availability of vaccines in a local or global outbreak scenario. The H1N1 influenza pandemic occurring in 2009/2010, several Ebola outbreaks in various African countries and finally the ongoing SARS-CoV-2 pandemic have impressively documented how vaccines produced with novel and unprecedented technologies can safely and effectively be applied.

The main reason for that success is defined through a regulatory system that is sufficiently mature to expedite licensure of emergency use vaccines without taking any shortcuts as regards the overall data base supporting licensure.

7. Rules and procedures governing medicinal products in the EU

The body of EU legislation in the pharmaceutical sector is compiled in Volume 5 of the publication "The rules governing medicinal products in the European Union":

Volume 1	EU pharmaceutical legislation for medicinal products for human use
Volume 5*	EU pharmaceutical legislation for medicinal products for veterinary use

*Please be aware that the provisions of the "EU pharmaceutical legislation for medicinal products for veterinary use" do not apply for the purpose of this White Book.

The basic legislation is supported by a series of guidelines that are also published in the following volumes of "The rules governing medicinal products in the European Union":

Volume 2	Notice to applicants and regulatory guidelines for medicinal products for human use
Volume 3	Scientific guidelines for medicinal products for human use
Volume 4	Guidelines for good manufacturing practices for medicinal products for human and veterinary use
Volume 6*	Notice to applicants and regulatory guidelines for medicinal products for veterinary use
Volume 7*	Scientific guidelines for medicinal products for veterinary use
Volume 8	Maximum residue limits
Volume 9	Guidelines for pharmacovigilance for medicinal products for human and veterinary use
Volume 10	Guidelines for clinical trial

*Please be aware that the provisions of the "EU pharmaceutical legislation for medicinal products for veterinary use" do not apply for the purpose of this White Book.

Special rules govern oversight of:

- Medicinal Products for Paediatric Use,
- Orphans,
- Herbal Medicinal Products and
- Advanced Therapies.

These rules and procedures are continuously adapted to novel products and novel challenges. Close collaboration with regulatory agencies around the globe, learned societies, public health institutions and most notably WHO ensures that scientific and regulatory standards set for the regulation of vaccines are equivalent to each other, provide convergent guidance and are interchangeable. As such, numerous WHO guidelines have replaced outdated EMA guidelines such as for example the WHO guidelines for the preclinical evaluation of (adjuvanted) vaccines (WHO, 2005, 2013).

The current evolutionary stage of commonly accepted regulatory and scientific guidance is marked by the recently released WHO guideline for mRNA-based vaccines impressively demonstrating that the global regulatory community increasingly relies on global rather than on regional regulatory standards (WHO, 2021).

This fundamental shift of paradigms successively introduced during the past decade forms the regulatory foundation required for ensuring vaccine equity for Africa in future.

8. The WHO schemes for globally ensuring safety and efficacy of vaccines

There are two WHO schemes for vaccines approval that aim to provide universal access to safe and high-quality medicines to all Member States:

- The WHO Prequalification scheme (PQ)
- The Emergency Use Listing (EUL)

It is important to highlight that both procedures, although aiming to reach the same goal namely to increase the access to vaccination, are in fact different procedures. In short, the EUL scheme is specifically tailored to public health emergency situations, like a pandemic, where data is likely to be limited and candidate vaccines cannot feasibly meet prequalification conditions, whereas the WHO PQ scheme is targeted at the long-term introduction and use of vaccines (GAVI). As part of the EUL, the WHO nonetheless expects a vaccine to be submitted for WHO PQ following full completion of vaccine development.

Both procedures are explained in more detail in the sub-chapters below.

8.1 The WHO Prequalification

8.1.1 The objectives of the WHO Prequalification scheme

The objective of the WHO vaccines prequalification (PQ) is to "**provide universal access to all relevant vaccines for all populations at risk**". Although WHO vaccines prequalification primarily benefits children: 2.5 billion doses of vaccines are administered to children under 10 each year worldwide and 65% of all babies worldwide are immunised using WHO-prequalified vaccines, it also provides great benefits to other population groups (WHO vaccines prequalification).

Essentially, the mission of WHO vaccines PQ is to advise United Nation (UN) procurement agencies, immunisation programmes, NRAs, and NCLs, as well as vaccine manufacturers and a range of organisations and networks, to ultimately enable WHO Member States to have access to high quality and reliable vaccines that meet their immunisation programme needs.

Although the inception of the PQ scheme took place already several decades ago (39th report of the WHO Expert Committee on Biological Standardization, Annex 1- Technical Report Series, No. 786, Geneva, WHO, 1989), the procedure itself evolved significantly over the years to accommodate sharply the increasing number and range of vaccines procured and distributed by UN agencies (revisions 1996, 2002, 2005 and 2012). The major role of the PQ procedure is to ensure that these vaccines are consistently safe and effective under conditions of use in national immunisation programmes.

In short, the WHO vaccines prequalification has:

- ensured that prequalified vaccines comply with WHO good manufacturing practice and good clinical practice and meet the operational packaging and presentation specifications of the relevant UN agencies,

- improved the health outcomes of national immunisation programmes by offering immunisation programme managers a list of appropriate products that are fit-for-purpose in challenging operating environments from which to select for procurement,
- facilitated introduction of a growing range of diverse vaccines thereby further accelerating achievement of international vaccine coverage goals,
- strengthened implementation of WHO standards for the quality, safety and efficacy of vaccines procured for immunisation programmes,
- ensured maintenance of product standards during the implementation of immunisation programmes through regular product re-assessment and targeted testing of samples,
- verified the capacity of NCLs to stringently verify vaccine compliance with the WHO Prequalification requirements,
- helped strengthening NRA capacity to provide crucial regulatory oversight for prequalified vaccines,
- monitored product quality and safety through investigation of any complaints and adverse events following immunisation that are received from immunisation programmes.

In prequalifying vaccines, WHO applies international standards to comprehensively evaluate and determine whether vaccines are safe and effective. WHO also ensures the continued safety and efficacy of prequalified vaccines through regular re-evaluation, site inspection, targeted testing and investigation of any product complaints or adverse events following immunisation. NRAs and NCLs play a vital role in the WHO vaccines prequalification scheme since they are responsible for regulatory oversight, testing and release of WHO-prequalified vaccines.

8.1.2 The WHO Prequalification eligibility

In general, the WHO Prequalification scheme is **eligible to any manufacturer of an already approved vaccine** who wishes to supply the product to WHO Member States. However, to apply for the prequalification assessment of a vaccine, several application criteria must be met:

1. **The vaccine is included on the vaccine's prequalification priority list.**

Vaccines that are eligible for WHO Prequalification are listed on the Vaccines Prequalification Priority List. The priority categorisation of vaccines is established by the WHO in consultation with the United Nation Children Fund (UNICEF) and the Revolving Fund of the Pan American Health Organization (PAHO), according to four levels of priority: high, medium, low and no priority (WHO/IVB/14.10). The range of vaccines that WHO prequalifies is based on a biennial prioritisation list that reflects public health needs in Member States' programmatic needs, and supply security (Vaccines eligible for WHO prequalification).

2. **The vaccine meets the mandatory characteristics for programmatic suitability (PSPQ).**

The assessment of suitability of the vaccine for use in a developing country should be in accordance with WHO/IVB/12.10. The assessment focuses on various criteria, with critical characteristics being vaccine vial monitor (VVM); anti-microbial preservative (absence, reduced concentration thiomersal or alternative preservative); and antigenic stability after reconstitution.

3. **The vaccine has received a marketing authorisation from the national regulatory authority of the country of manufacture.**

The relevant NRA must have granted either a marketing authorisation or an emergency use authorisation for the vaccine. So far, no COVID-19 vaccine has been prequalified by the WHO yet.

4. **The NRA responsible for vaccine regulatory oversight is a WHO-listed authority or functional NRA.**

All vaccines that were assessed by functional NRAs (Maturity Level 3, ML3 or above) are automatically eligible for PQ vaccines assessment. Furthermore, vaccines assessed by a WHO-listed authority (WLA) are also eligible for abridged assessment for PQ of vaccines (COVAX product eligibility). According to the latest guidance "A regulatory authority or a Regional Regulatory System (RRS) will need to meet the relevant GBT ML4 indicators for those regulatory functions and product categories for which it requests to be listed as a WLA (i.e., the scope of its WLA listing)" (Evaluating and publicly designating regulatory authorities as WHO listed authorities, WHO, 2021).

- Prequalification following functional NRAs assessment

Oversight by a functional NRA is used as one of the conditions for manufacturers of vaccines to apply for prequalification (Eligibility to apply for PQ, TRS978, Annex 6, section 2). WHO does not process an application until the WHO NRA assessment is conducted and the outcome is satisfactory. These functional NRAs will then collaborate with PQ, as well as exercise oversight of the prequalified vaccine, including production and lot release. Nevertheless, as opposite to the streamlined procedure, a vaccine undergoes full assessment by WHO PQ, in accordance with the procedure described in Section 8.1.3.

The current list of functional NRAs is available (WHO), compiling those countries that were assessed based on evaluation tools before the GBT was developed for vaccines. This will be replaced in the future with NRAs at ML3 for vaccines following assessment based on the GBT.

- Streamlining assessment (abridged assessment)

The abridged assessment is an abbreviated PQ process that envisages enhanced reliance on the oversight performed by the responsible NRA, when the NRA exhibits a high level of performance of WHO's regulatory functions and exercises full regulatory oversight of any given vaccine (WHO-TRS- 978 Annex 6). This system is based on enhanced support to WHO during the PQ of pandemic H1N1 influenza vaccines and establishment of collaboration agreements in the evaluation and ongoing regulatory oversight of vaccines of interest.

In case of this streamlined procedure, the WHO explicitly requests the assistance of the NRA responsible for the regulatory oversight of the candidate vaccine and engages in discussions for the establishment of a formal collaboration agreement that outlines the shared understanding of roles, responsibilities and commitments of each party. The scope of this agreement can be determined by both parties and could include one or more of the following (each subject to agreement by the manufacturer): sharing of NRA reports relevant to product quality, nonclinical and clinical evaluation; sharing of NRA/NCL test results (including the raw data); sharing of inspection reports.

Until WHO has a list of NRAs that have been assessed and designated as the WLA for vaccines, through the use of the GBT and performance evaluation, WHO-TRS- 978 Annex 6 provides for

reliance on these NRAs that provided support to WHO during the PQ of pandemic H1N1 (2009) influenza vaccines, the full list currently stands as follows:

- Australia – TGA.
- Belgium – FAMHP.
- Canada – Health Canada.
- EU – EMA.
- France – ANSM.
- Germany – PEI.
- Italy – AIFA.
- Netherlands – MEB.
- Switzerland – Swissmedic.
- United Kingdom – MHRA.
- United States of America-US FDA.

In the case of EU, the mandate for approval of new vaccines mostly lies with EMA and therefore mostly EMA is the competent EU authority as regards the above list.

8.1.3 Steps of the PQ procedure

The procedure is initiated by the manufacturer with a request for a pre-submission meeting to advice WHO on the intention to submit a vaccine for evaluation. Next, if the conditions for acceptance are fulfilled according to eligibility criteria described above, the manufacturer submits an application letter to WHO providing specific details, such as country and manufacturing sites, licensing status, presentations put forwards for procurement and expected deadline for dossier submission.

A manufacturer whose application letter is accepted submits a Vaccine Prequalification Dossier (VPQD). Next, WHO screens the VPQD for completeness and compliance with the required format and contents. The assessment of the programmatic suitability of the vaccine candidate for WHO Prequalification is also done at this step. The assessment of the dossier is performed following the WHO Prequalification procedure for assessing the acceptability, in principle, of vaccines for purchase by UN agencies (WHO TRS 987, Annex 6), as well as verification of compliance of the manufacturing site with the WHO Good Manufacturing Practices by means of inspection, where necessary.

WHO requests the manufacturer to submit vaccine samples for independent and initial testing. The testing of these samples is performed by WHO contracted and qualified collaborative laboratories.

An inspection of the vaccine manufacturing site is performed to assess that the vaccine complies with the WHO recommendations for production and quality control, that it meets UN tender specifications, if the company has an adequate quality management system in place, and that the relevant vaccine is manufactured in compliance with the WHO Good Manufacturing Practices (GMPs).

Vaccines that are considered to be fully compliant with the WHO Prequalification requirements are included on the WHO List of Prequalified Vaccines. The summary of the assessment of data and information submitted by the manufacturer is provided then in a WHO Public Assessment Report (WHOPAR) and a WHO Public Inspection Report (WHOPIR). These documents describe

the quality, safety, and efficacy of the prequalified product. The WHOPAR will summarize the assessment of the product information that was submitted in the product dossier. The structure and format of the WHOPAR are adapted from the European Public Assessment Report, as published by EMA, to serve the requirements of the WHO medicines prequalification (Section Guidance for Part 6 Scientific Discussion of a WHO Public Assessment Report, Section Guidance for Part 3 Patient Information Leaflet (PIL) of a WHO Public Assessment Report, Section Guidance for Part 4 — Summary of Product Characteristics (SmPC), Section Guidance for Part 5 Labelling of a WHO Public Assessment Report). The WHOPIR(s) will provide the date, duration and scope of the inspection, and a summary of the observations and findings of the inspection(s).

Posting of the WHOPAR and WHOPIR(s) generally occurs sometime after inclusion of the relevant product in the WHO List of Prequalified Vaccines. This is because their contents must be agreed with the manufacturer. In this way, WHO ensures that confidential information is not disclosed.

8.1.4 Post-Listing

To ensure continued acceptability of prequalified vaccines a rigorous post-prequalification process is also conducted. It consists of the evaluation of activities related to the performance of the vaccine and its manufacturer. This is done annually through the evaluation of a Prequalification Annual Report (PQVAR), which includes a summary of changes on the product, report of complaints or adverse events following immunisation (AEFIs), etc for moderate variations (type R). In addition, the post-prequalification process includes the reporting of major variations, which includes manufacturing/facility changes, to be approved by WHO before implementation for United Nations´ supply (type A) (Guidance on Variations to a Prequalified Vaccine). Targeted testing of vaccines lots is also carried out to monitor compliance with product standards.

8.2 The Emergency Use Listing

8.2.1 The objectives of the Emergency Use Listing procedure

The EUL procedure was developed to adequately address public health emergency situations, like a pandemic, where data is likely to be limited and candidate vaccines cannot feasibly meet prequalification conditions (e.g., candidate vaccines are not yet licensed). Whereas the WHO PQ is targeted at the long-term introduction and use of vaccines, the circumstances characterising emergency situations – especially high morbidity and mortality rates – need a quicker pathway to confer unlicensed vaccines into a conditional approval within the shortest possible period for public delivery and use. The primary objective of the EUL is therefore to ensure that safe, effective, and good quality vaccines are made available as quickly as possible to effectively address a serious public health emergency. It is important to reiterate that the EUL procedure is therefore not an alternative to the WHO PQ scheme, as it is an entirely different process. It is intended to provide a time-limited listing for unlicensed products in an emergency context when only limited data are available, and the products are not yet ready for full application for prequalification. **Importantly though, as part of the EUL, the WHO nonetheless expects the vaccine to be submitted for WHO PQ following full completion of vaccine development.**

EUL is a relatively new procedure – the WHO developed the Emergency Use Assessment and Listing mechanism in response to the 2014 – 2016 Ebola Virus Disease outbreak. The EUL is a risk-based procedure for assessing and listing unlicensed:

- vaccines,
- therapeutics,
- and in vitro diagnostics (IVDs),

for use primarily during public health emergencies of international concern (PHEIC) but also in other public health emergencies, if appropriate.

The procedural aspects were recently revised and the new EUL procedure was published in December 2020 (Emergency Use Listing procedure).

8.2.2 The EUL eligibility

There are several criteria that must be met by the manufacturer to be able to participate in the scheme:

- The disease for which the product is intended is serious or immediately life threatening, has the potential of causing an outbreak, epidemic or pandemic and it is reasonable to consider the product for an EUL assessment, e.g., there are no licensed products for the indication or for a critical subpopulation (e.g., children).
- Existing products have not been successful in eradicating the disease or preventing outbreaks (in the case of vaccines and medicines).
- The EUL is not intended to interfere with ongoing clinical trials. This means that the clinical development should proceed as planned after the initial submission and subsequent updates.
- The applicant is obliged to complete the development of the product and apply for WHO Prequalification once the product is licensed.
- The product is manufactured in compliance with current GMP in the case of medicines and vaccines.

8.2.3 The EUL procedure

There are 3 phases of the EUL procedure:

- Pre-emergency phase
- Emergency phase, and
- Post-listing phase

WHO established a set of activities that can be already undertaken prior to the occurrence of an emergency, such as the selection of experts that will form the:

- PHO- WHO Product Evaluation Group,
- TAG-EUL- Technical Advisory Group for Emergency Use Listing.

As all activities are time critical many of them should be shifted to the pre-emergency phase. Nevertheless, in case the pandemic is already ongoing, this approach can no longer apply. As with the current ongoing SARS-CoV-2 pandemic all activities for COVID-19 related products intended to be developed using this scheme will be moved to the emergency phase.

Emergency phase procedure:

1. An application letter is sent to WHO's Director of Regulation and Prequalification Department, copy to the relevant Prequalification Team and the NRA responsible for the regulatory

oversight of the unlicensed product (according to the WHO template). WHO will acknowledge receipt of the application letter by email, with a copy to the relevant NRA. The acceptance of an application will also be confirmed by email, with a copy to the NRA. WHO will only respond with an official letter in those cases where the product cannot be accepted because it does not meet the eligibility criteria. WHO will endeavour to advise the applicant and the NRA of a rejection of the application within 2 weeks of receipt of the official request.

2. Once the product has been accepted for review under the EUL procedure, the applicant will be required to submit a duly signed Letter of Agreement (as per WHO template) together with the dossier in the appropriate format (as per WHO template). Once the product has been considered eligible for assessment under the EUL procedure, the Prequalification Team Group Lead of the relevant product stream will designate a focal person for the EUL assessment of a specific product.

4. The focal person will perform the screening of the submission to ensure that sufficient information is available to initiate the assessment by the WHO Product Evaluation Group (PEG) based on the essential data requirements (as per WHO template). If the screening indicates that the assessment cannot start due to lack of information, this will be communicated to the applicant. A complete dossier may be submitted any time afterwards.

5. The focal person will then coordinate the distribution of the submitted data package to the members of the PEG, provide specific instructions for the review as appropriate, and manage communications with the applicant.

6. A consolidated report of the PEG (as per WHO template) will indicate whether the information received is considered sufficient for a recommendation, or if additional information is needed prior to giving a recommendation. The report of the PEG and all subsequent versions with updates will be submitted to WHO. WHO may submit this report to the Group responsible for a final recommendation on possible listing (TAG-EUL).

8. The recommendation of the TAG-EUL will be used by WHO to decide whether or not the product can be granted an EUL. It is important to note that the TAG-EUL may request further information from the applicant before making a recommendation.

9. Upon making a decision whether or not to grant a recommendation (acceptance or non-acceptance) for EUL of the evaluated product, WHO will (without prejudice to any confidential information of the applicant/manufacturer) publish information about the product in a public report available on a dedicated portal of the WHO website. This may include negative assessment outcomes.

10. The validity of an EUL in the context of a PHE will generally be for 12 months. When deemed necessary, the EUL can be extended.

It is important to note that the WHO Member States have the sole prerogative to use the EUL as the basis to authorise the use of an unlicensed vaccine/medicine/IVD at the national level.

Similar to the PQ procedure, the assessment pathway under the EUL procedure will be based also on either abridged or a full review process. Again, similarly as for PQ, the abridged pathway is possible when the assessment of the product is performed by WHO-listed Authorities (list available here). Reports of the inspections conducted by the WLA that issued the authorisation under

extraordinary circumstances such as a public health emergency will also be considered to waive the requirement for an inspection by WHO.

Post-listing phase:

After a product has been listed, WHO will continuously monitor field reports on safety surveillance, efficacy, and quality complaints about the COVID-19 vaccine – all of which may impact the validity of its EUL status. The COVID-19 vaccine manufacturer will also continue generating additional clinical data from vaccine trials and deployment to enable full licensure and WHO Prequalification of its vaccine.

8.2.4 COVID-19 and WHO vaccine schemes

In light of the ongoing SARS-CoV-2 pandemic, WHO published a detailed guidance that provides advice to manufacturers on both the process and the criteria that will be used by WHO to evaluate COVID-19 vaccines that are submitted either for prequalification (PQ) or for EUL (Considerations for Evaluation of COVID-19 Vaccines, November 2020).

Since COVID-19 has been declared a global pandemic with no existing vaccines, any vaccine against COVID-19 developed in compliance with current GMPs are currently eligible for an EUL, and none for PQ procedure.

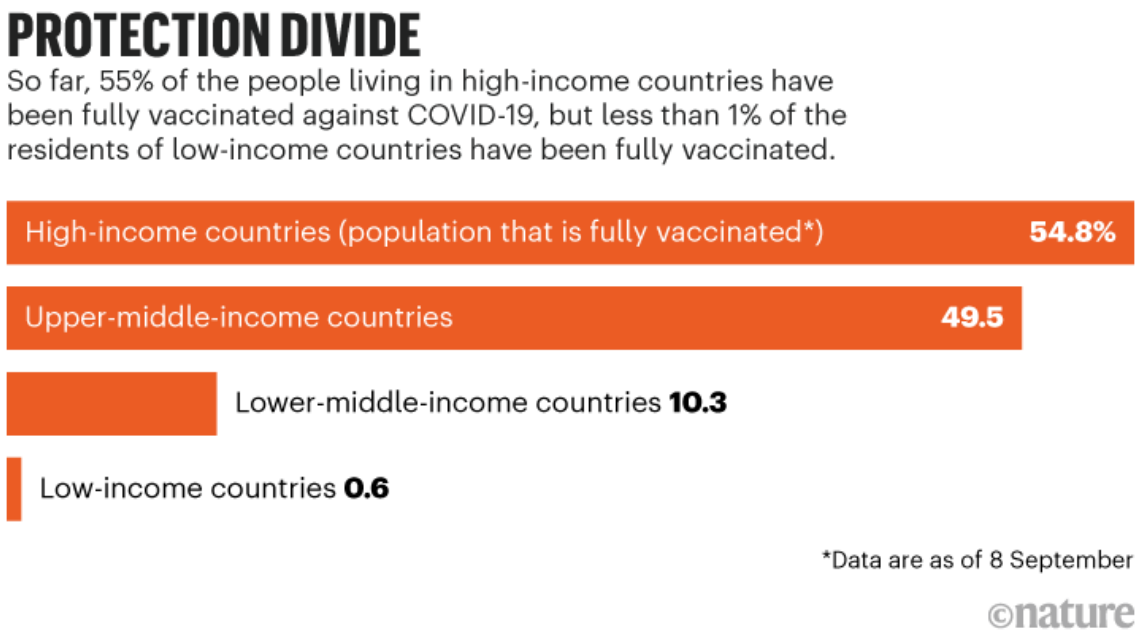
Nevertheless, as mentioned before, EUL is intended to provide only a time-limited listing for unlicensed products in an emergency context when limited data are available and the products are not yet ready for application for prequalification. As such, it is expected that the manufacturer will complete the development of the product and submit for licensure and WHO Prequalification.

In December 2020, the Pfizer/BioNTech vaccine against COVID-19 became the first vaccine to be granted an EUL from the WHO. This opened a pathway for countries who are yet to approve the vaccine to expedite their own national regulatory approval processes for it and for Gavi, alongside its Alliance partners, to procure and distribute the vaccine to participating countries through the COVID-19 Vaccines Global Access (COVAX) initiative, a global risk-sharing mechanism for pooled procurement and equitable distribution of COVID-19 vaccines. A full list of COVID-19 vaccines enrolled within WHO EUL/PQ evaluation process is available here.

9. Simplification of reg and tech transfer through the employment of regulatory standards jointly developed by EMA, national regulatory agencies and WHO, creating a functional and globally accepted regulatory system

Despite many efforts to speed up the vaccine uptake around the globe, as of Q3 2021 we are far from obtaining satisfactory results. Vaccines against COVID-19 are not reaching many people in the Low- and Medium-Income Countries (LMIC), despite donations from wealthy nations. So far, only less than 5% of people in low-income countries are fully vaccinated, and just 10% are in LMIC, compared with more than half in high-income countries. Although several vaccines, including BioNTech's mRNA vaccine have already granted EUL status, and vaccines procurement and distribution though COVAX is already ongoing, more concerted efforts are necessary to secure universal access to COVID-19 vaccines worldwide (Maxmen, 2021; Padma, 2021).

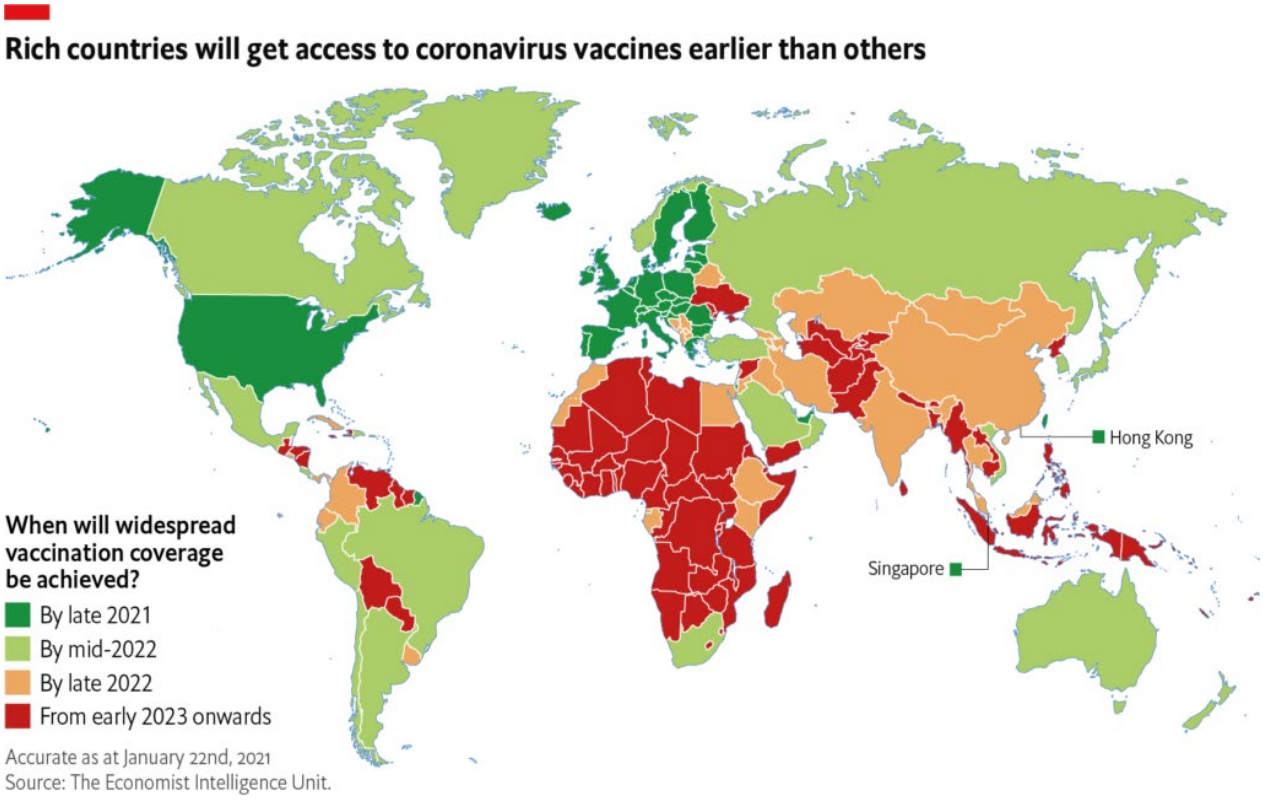
Figure 1: Protection divide (reprinted from Nature (Maxmen, 2021))



The original plan of COVAX was to deliver two billion doses of safe and effective vaccines that have passed regulatory approval and/or WHO Prequalification by the end of 2021. It was predicted that countries participating in the COVAX Facility, will benefit from the assurance that the facility can supply them with enough vaccine doses to immunise up to 20% of their country's population. These vaccines should be offered equally to all participating countries, proportional to their populations, initially prioritising healthcare workers and then expanding to cover vulnerable groups, such as the elderly and those with pre-existing health conditions. Further doses will then be made available based on country need, vulnerability and COVID-19 threat. The COVAX Facility also plans to maintain a buffer of doses for emergency and humanitarian use (WHO, 2020). For lower-income countries, the cost of vaccines will be co-financed through development aid and philanthropic organisations (Herlitz et al., 2021; Hinson et al., 2021).

However, despite these efforts, the doses delivered through COVAX will not be sufficient to achieve widespread coverage in a timely manner. In fact, it has been estimated that most lower-middle-income countries will not achieve widespread coverage until late 2022 or even early 2023 (Unit, 2021). This is due to multiple reasons, one of the major ones being embargo on export of SARS-CoV-2 vaccines produced in India following an unprecedented outbreak of the pandemic in that geographical region. As a result, one of the major suppliers of the COVAX, the largest vaccine manufacturer of vaccines in the world, the Serum Institute of India (SII) was unable to deliver their agreed vaccines quota. Because of issues including the export pause and a lack of donations, COVAX has shifted its goal of delivering two billion doses from this year to 2022 (Maxmen, 2021).

Figure 2: Timelines for rollout of coronavirus vaccines worldwide, reprinted from (Unit, 2021)



This map depicts the latest forecasts from The EIU for the rollout of coronavirus vaccines, reflecting the time when countries may expect to have vaccinated the majority (60-70%) of their adult population. Criteria considered include supply deals, production constraints, vaccine hesitancy, the size of the population, and the availability of healthcare workers. The data are also adjusted by analysts to reflect specific conditions on the ground.

This, and many reasons behind delays in vaccinating populations in LMIC prompted many experts to believe that the best way to ensure equitable access to COVID-19 vaccines is to enable countries in LMICs to make their own vaccines. “Charity is good, but we can’t rely on charity alone,” says Peter Singer, an adviser to the Director General of the WHO (Maxmen, 2021).

Therefore, it is very important that pharmaceutical companies and governments that developed highly effective vaccines will find the most effective and time-saving solutions to share their patented knowledge and technology with organisations or drug manufacturers that could produce these vaccines locally in Africa.

10. The particulars of vaccine manufacturing

Compared to pharmaceuticals, the global vaccine market is unique since most of the global sales volume are purchased on a tender basis by large governmental and non-governmental organisations rather than on the private market by individuals (UNIDO, 2017). As such, the vaccine market is not a free and open market, which has significant bearing on the viability of vaccine production and hence the need for consideration during the initial phase of a project´s feasibility analysis.

Most procurement of vaccines on a global level is conducted through the United Nations Children´s Fund (UNICEF), purchasing on behalf of donor organisations such as Gavi (UNIDO, 2017). Gavi and similar organisations fund vaccine purchases on behalf of the poorest countries. Selling to UNICEF requires WHO Prequalification, which is typically a high barrier for a newcomer. Prequalification is an assessment by the WHO of the product to ensure the safety, the appropriateness and that stringent quality standards are met. Manufacturers wishing to enter this large market need to meet most stringent prequalification criteria. Moreover, the associated country´s NRA needs to have reached a high level of maturity/accreditation.

Lastly, in comparison to other pharmaceutical products, vaccine manufacturing faces relatively high costs, long timelines, and significant barriers to entry.

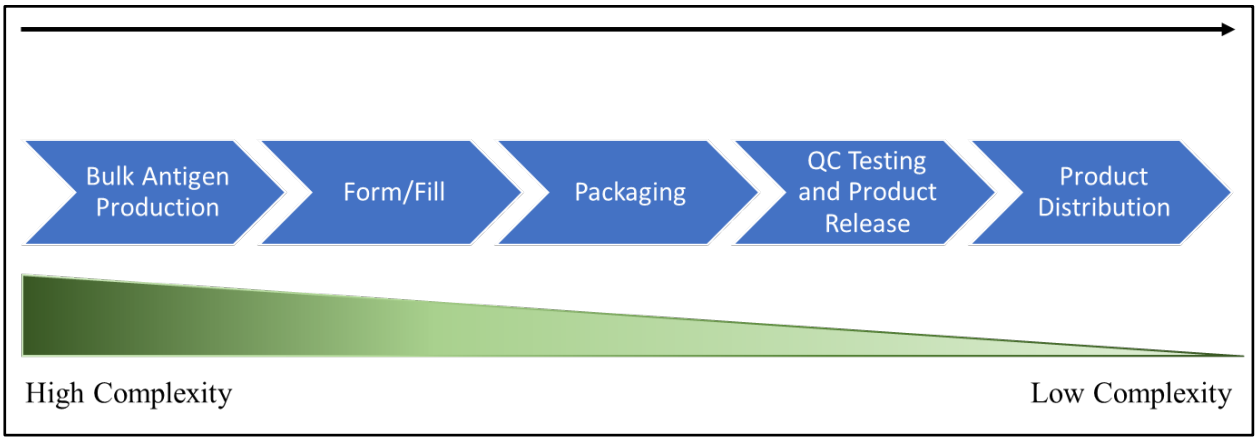
Steps of Vaccine Manufacturing Production

Compared to the manufacturing of pharmaceuticals, the manufacturing process for vaccines is much more complex and necessitates the use of highly specialised facilities and equipment. Whereas pharmaceutical production requires a series of relatively well-understood chemical reactions and physical manipulations, vaccine production involves complicated biological synthesis steps that are often not fully understood.

Vaccine production often relies on the ability to demonstrate that a certain production process, which has yielded a product shown to be efficacious through clinical trials, can be repeatedly followed and controlled. In addition, many of the sterilisation methods in the manufacturing process (such as sterilisation of the final product in a vial or ampoule via autoclave) are not possible for vaccines.

In general, vaccine manufacturing involves steps illustrated in Figure 3.

Figure 3: Key vaccine manufacturing steps, reprinted and adapted from (UNIDO, 2017)



First Step: Bulk Antigen Production

Due to the complexity of the process, bulk antigen production is the most cost-intensive step in the chain of vaccine manufacturing processes (UNIDO, 2017). Except for mRNA- and vector-based vaccines, vaccine antigens are extracted from biological starting materials containing or expressing them (Table 1). The antigen is then harvested and isolated via purification processes involving centrifugation, chromatography and/or filtration resulting in purified antigen, with the exact processes vary between vaccines.

Table 1: Complexity of bulk antigen production based on the materials and the effects on vaccine manufacturing, reprinted and adapted from (UNIDO, 2017)

Key factors	**Low** **Complexity of Production** **High**			
Speed	Mammalian	BEVS/insect cell	Yeast	Bacteria
Cost	Bacteria	Yeast	BEVS/insect cell	Mammalian
Typical yield	Mammalian	BEVS/insect cell	Bacteria	Yeast
Post-translational modification	Bacteria	Yeast	BEVS/insect cell	Mammalian
Regulatory approval	BEVS/insect cell	Yeast	Bacteria	Mammalian

Abbreviations: BEVS= Baculovirus Expression Vector System.

Second Step: Formulation/Fill (Form/Fill)

The purified antigen (drug substance) then undergoes formulation, which might include combination with adjuvants to enhance immune responses, combination with stabilisers to ensure the product remains potent until it is administered, and combination with preservatives to ensure sterility over the entire course of administration to multiple individuals. The formulated drug substance, i.e., the DP, is then filled into vials, plastic tubes, ampoules, or syringes. Each filled vaccine must be visually inspected to ensure its physical integrity and that the vaccine is free of noticeable foreign particles and there are no issues with the product´s appearance.

Vaccines, which are not stable as liquids at room temperatures, are lyophilised, meaning that the vaccine must be distributed with appropriate diluent so it can be reconstituted later, prior to administration. Lyophilisation is a complex process which will further contribute to additional cost for vaccine manufacturer.

Third Step: Packaging, Cold Chain and Distribution

Subsequently, the filled and inspected vials are packaged, undergo final quality control release testing (the last step of the QC process, since QC tests occur throughout the above processes as well) and be distributed. The quality control tests include analysing a sample of the finished product to ensure it has the required potency, purity, concentration of key ingredients and sterility.

Product Registration and Clinical Trials

Unlike pharmaceuticals, where a copy of an existing drug can be approved without clinical trials (generic drugs), in most cases vaccines require the full-fledged phase I, II and II clinical trials process to demonstrate safety, immunogenicity and efficacy.

10.1 Challenges for newcomers to vaccine production

Due to the complex nature of vaccine production, there are several challenges facing new manufacturers (UNIDO, 2017). Summaries of the various challenges facing new manufacturers in producing vaccine are provided below:

- Initial Investment.
  Significant capital for a commercial production facility is required.
- Operating Costs.
  The complex nature of vaccine production results in high operating costs, especially for raw materials, skilled personnel and to continuously operate the utilities and clean rooms.
- Project Durations.
- Industrial Cluster.
  The lack of other vaccine manufacturers in the region results in issues related to supplies, skilled workers, and technical support.
- Competition.
- Limited Partnership Opportunities.
- Hiring and Training Personnel.
- Changes to the Landscape Over Time.

10.2 mRNA vaccine manufacturing

During the currently ongoing COVID-19 pandemic, mRNA vaccine technology has been one of the forefront technologies of choice in development of COVID-19 vaccine. One of the most important advantages of mRNA over conventional vaccines is its relatively simple manufacturing. mRNA is produced in a cell-free system and uses no animal derived materials. As such, cell-derived impurities or adventitious contaminations are absent, which contributes to safer manufacturing of these molecules (Pardi et al., 2018; Rosa et al., 2021).

Although a well-established manufacturing platform is currently still lacking, several combinations of steps are possible, and can be grouped as:

- Upstream processing, which consists of the enzymatic generation of mRNA.
- Downstream processing, which consists of the unit operations required to purify the mRNA product.

Briefly, the generation of mRNA involves *in vitro* transcription (IVT) enzymatic reaction relying on T7, SP6 or T3 RNA polymerases to catalyse the synthesis of the target mRNA from the corresponding DNA template (Pardi et al., 2018; Rosa et al., 2021). The production of mRNA can be performed in either a one-step enzymatic reaction, where a capping analogue is used; or in a two-step enzymatic reaction, where the capping is performed using a vaccinia virus derived capping enzyme (Rosa et al., 2021).

Once, the mRNA is generated, i.e., the completion of the upstream processing, the mRNA must be isolated and purified from the reaction mixture using multiple purification steps to achieve clinical purity standards. The reaction mixture contains not only the desired mRNA product, but also several impurities, which includes enzymes, residual nucleoside triphosphates (NTPs) and DNA template, and aberrant mRNAs formed during the IVT.

The application of mRNA vaccines has until recently been restricted by the instability and inefficient *in vivo* delivery of mRNA. However, the embedding of mRNA into lipid nanoparticles (LNPs) has resulted in successful development of stable and efficacious mRNA vaccines against COVID-19. The key aspects of LNPs, which confer improved vaccine delivery are:

- The ability to control and target payload release.
- Stabilisation of entrapped pharmaceutical from a hostile environment.
- The ability to encapsulate high pharmaceutical content (in comparison to other carrier systems).
- Increase of the bioavailability.
- The ability to transport across cellular membranes.

10.3 Viral protein vaccine manufacturing

Recombinant or purified protein vaccines are based on the concept that humoral immune responses mounted to an infection are often targeted toward specific localised regions on the surface of protein antigens known as epitopes.

The recombinant proteins for vaccination are produced by expressing these immunogenic proteins using heterologous expression systems. The immunogenic protein antigens can also be purified from the infectious organism. *Escherichia coli* (*E. coli*), *Saccharomyces cerevisiae* (*S. cerevisiae*), or baculovirus-insect cells are established recombinant expression systems for foreign protein production (Cid & Bolívar, 2021).

In general, the gene of interest is inserted into an expression vector that was capable of directing the synthesis of large quantity of the protein of interest. The recombinant cells expressing protein of interest are grown in fermenter. At the end of the fermentation process, the protein of interest is harvested by lysing the cells. The protein of interest is then purified by a series of physical and chemical methods. The purified protein then undergoes final formulation (Gomez et al., 2013).

10.4 Viral vector-based vaccine manufacturing

Viral vector vaccines work by cloning the antigen of interest into a heterologous virus that will serve as a vector to deliver the foreign gene inside the host cells, leading to its expression. The main advantage of viral vector vaccines is that they often provide long-lived immunity, including humoral antibodies, secretory antibodies, and cytotoxic T cells (Ura et al., 2014).

The specific properties of the vector are determined by the virus from which it is derived., with each vector having distinct advantages and disadvantages (Table 2). Adenoviruses are the most used for human vaccines because they are infectious to various cell types, and they show

efficient transgene expression, high *in vitro* growth, lack of genome integration and genetic stability.

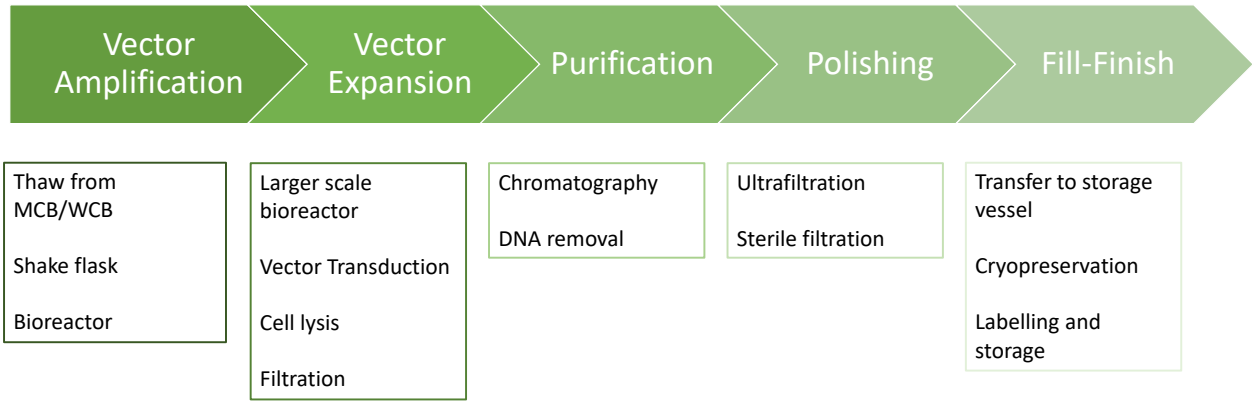
Table 2: Advantages and disadvantages of major viral vectors (Ura et al., 2014)

Virus	Advantages	Disadvantages
Retrovirus	• Long-term gene expression	• Generation of replication-competent virus • Potential for tumorigenesis • Infect dividing cells only
Lentivirus	• Long-term gene expression • Infects non-dividing and dividing cells • High immunogenicity	• Generation of replication-competent virus • Potential for tumorigenesis
Vaccinia virus	• Safety • High titre production • High immunogenicity	• Pre-existing immunity
Adenovirus	• Safety • High titre production	• Pre-existing immunity
Adeno-associated virus	• Long-term gene expression • Non-pathogenic virus • Induces a unique CTL response	• Low titre production • Pre-existing immunity
Cytomegalovirus	• Protects against SIV infection in an animal model	• Risk of pathogenesis in specific individuals
Sendai virus	• High immunogenicity	• Pre-existing immunity

Abbreviations: CTL= Cytotoxic T Lymphocytes, SIV= Simian Immunodeficiency Virus.

The first step in manufacturing of viral vector-based vaccine manufacturing involves packaging of the gene of interest into a delivery vehicle, i.e., a viral vector, followed by expansion of its host cell lines to produce high concentration of the vector. The collected vector is then purified, polished and transferred to fill-finish (Figure 4).

Figure 4: Overview of a standard viral vector manufacturing process (Pettitt et al., 2016)



10.5 Inactivated vaccine manufacturing

Inactivated vaccines are a well-established technology used over the last 100 years to vaccinate billions of individuals, including for seasonal flu, hepatitis A, polio and rabies. In an inactivated vaccine, the virus is killed but the whole virus envelope is preserved so compared to vaccines targeting only the spike protein, inactivated vaccines have the potential to provide an added benefit by boosting T-cell responses against additional SARS-CoV-2 proteins.

In general, the pathogen is first cultivated on a substrate to produce large quantities of antigen. Historically, vaccine manufacturers have been using primary cells, tissues, fertilised eggs, and even whole organisms as substrates for virus propagation. Today, vaccine manufacturers are increasingly shifting toward virus growth on continuous cell lines (Sanders et al., 2015).

Once the virus has been propagated, it is often purified and concentrated prior to inactivation. The purification methods used include ultrafiltration, size-exclusion chromatography (SEC) and sucrose gradient centrifugation. Inactivation can be performed using chemical or physical methods or a combination of the two.

Inactivated vaccines possess a higher safety profile as compared to live vaccines. In addition, inactivated vaccines are generally less reactogenic, relatively straightforward, and technically feasible to produce with fewer regulatory hurdles for licensure. However, inactivated vaccines are typically associated with a lower immunogenicity, which can imply the necessity of multiple doses or adjuvant addition, which consequently raises the costs of goods and vaccine pricing. Hence, choosing an inactivated vaccine approach is in general a trade-off between increased safety and a fast pathway to regulatory approval on one hand, and the risk of reduced antigenicity of the immunogen on the other hand, which often requires adjuvant addition and/or multiple doses.

11. Roles and responsibilities of the EU, African institutions and WHO in reg and tech transfer efforts

A country in which vaccine manufacturing capacity is being built should have appropriate:

- Technical skills,
- Quality Management System,
- Market,
- Political commitment,
- Ability to ensure adherence to international quality standards.

Due to the complexity of vaccine manufacturing and the required stringent regulatory oversight, collaboration among different stakeholders is necessary to ensure successful regulatory and technology transfer to Africa. A study, based on literature review and questionnaires on global vaccine stakeholders, African governments, and regulatory authorities, was published in 2019 investigating how investment for vaccine production in Africa could be triggered and in which way it could be affordable to most African governments or investors (Makenga et al., 2019).

11.1 African governments

In response to the survey questionnaires in the abovementioned study (Makenga et al., 2019), four African governments, out of 14 contacted, responded and were interested in the establishment of vaccine manufacturing capacity in their country. However, they would do this only with an external financial and/or technical capacity building support. In general, the African governments which responded are willing:

- To support investors at varying levels, such as land, tax incentives, infrastructure provision, and monetary support as a private public partnership.
- To facilitate necessary extra capacity building in their NRA in a form of training.
- To support collaboration with competent authorities of other countries and the WHO.

The WHO would help African governments during an interim phase to cover all regulatory aspects around vaccine manufacturing facility establishment and at the initial stage of product life cycle. In return, all the African governments that responded expect access to a vaccine at an affordable price and establishment of employment for native experts.

11.2 National Regulatory Authorities

Capacity gaps of NRAs in Africa vary from country to country. A minimum maturity level of 3 (ML3) is necessary for an NRA to be considered as a fully functional regulatory authority. Importantly, currently, two African countries: Ghana and Tanzania have already reached ML3, paving the way forward for other African States. In order to reach ML3, most NRAs of African counties would mainly need capacity building in relation to:

- Qualification of GMP inspectors.
- Quality control laboratories for vaccine.
- Technical expertise to perform lot release.

An efficient and reliable regulatory system is prerequisite for the WHO Prequalification programme for vaccines, as the NRA assessing providing oversight of a product applying for prequalification must be operating at an acceptable level of maturity. As part an effort to improve the regulatory capabilities of various NRAs, WHO has developed a GBT as part of its five-step capacity building programme to assist NRAs in order to formulate an effective and workable Institutional Development Plan (IDP).

Varying time would be required to fill the capacity gaps. Eleven NRAs, out of 22 contacted, responded to the questionnaires and are willing to collaborate and rely on WHO and other competent NRAs from other countries to cover the interim period for regulatory need of vaccine manufacturing and batch release oversight (Makenga et al., 2019). With regard to global vaccine supply from an African country, some have already established regional regulatory collaboration, such as the East African Community´s (EAC) Medicines Regulation Harmonisation (EAC).

11.3 Multinational companies

Experts from multinational companies surveyed and highlighted the importance of significant incentives such as benefit of conducting business in a politically stable environment, ease of conducting business activities, ease of regulatory navigation along the development and licensure roadmap, and tax incentives in the long term (Makenga et al., 2019).

11.4 The European Union

Support would be offered by individual Member States of the EU, such as the Paul Ehrlich Institute (PEI) in Germany, as well as non-EU partner agencies, such as Health Canada. In addition, EU could provide support via Article 58 procedure of Regulation (EC) No 726/2004 (European Commission, 2004).

Article 58 of Regulation (EC) No 726/2004 provides a mechanism whereby EMA may give a scientific opinion, in collaboration with the WHO, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the EU (European Commission, 2004). The aim of this procedure is to facilitate patient access to essential medicines in LMIC, including new or improved therapies for unmet medical needs, which are intended to prevent or treat diseases of major public health interest.

It must be noted that despite the support from EU and other partner states, it is imperative to develop an independent and comprehensive regulatory framework in line with ICH requirements in order to achieve the goal of reaching vaccine manufacturing autonomy in Africa.

12. Preparation, conduct and completion of successful reg and tech transfers – requirements and principles

Equal access to a COVID-19 vaccine is the key to end this current pandemic, in accordance with the rule “nobody is safe until everybody is safe.”

As of Oct 2021, the SARS-CoV-2 pandemic is still ongoing and effective COVID-19 vaccines are urgently needed, specifically in countries with very low vaccine coverage. As mentioned in this White Book before, currently only approximately. 4-5 % of people in Africa are fully vaccinated and only 15 out of 54 countries have achieved the WHOs 10% target for 2021. Alarmingly, half of the countries on the African continent have vaccinated less than 2% of their population and two countries did not roll out their vaccine campaign yet.

As such, it is a matter of utmost importance to establish a system which might help to alleviate the vaccine gap between the high- and LMIC.

One of the most apparent solutions is to increase vaccine manufacturing capacity and re-location of manufacture to countries with low vaccine coverage to ensure more equitable distribution. Nevertheless, despite all currently ongoing efforts initiated by AU, African CDC, WHO and others, most African countries will not be able to establish a fully functional infrastructure enabling immediate vaccine production and control. This is mostly due to:

- insufficient- or lack of experience with vaccine manufacturing, and
- insufficient- or lack of mature regulatory system.

It is important to highlight that worldwide, the medicinal products regulations and regulatory activities are becoming more and more globalized. While harmonisation and convergence have been pursued for many years through international initiatives, the use of reliance is an emerging trend as a strategy to bring efficiencies to regulatory systems. The principle of reliance is central to WHO’s approach to regulatory systems and was a base to develop procedures such as PQ and EUL (please refer to Chapter 8.1 and 8.2).

Similarly, such a principle of reliance could be extended to licensures obtained in countries and regions with mature regulatory systems such as Germany, France, US, EU etc. Importantly, as mentioned before, several SARS-CoV-2 vaccines currently hold EUL status (WHO, 2021), which further highlights that these products and technologies were developed not only in accordance with the standards of the manufacturing country but are also fulfilling the criteria defined by WHO.

Of course, re-location of manufacture to African continent will not be trivial as it requires a lot of commitments and actions from various stakeholders. However, examples of such successful transfers are already available, e.g., the Russian Sputnik V vaccine was broadly licensed to 34 drug companies outside Russia, including several in India and Brazil (Maxmen, 2021).

According to the Russian manufacturer, handing off Sputnik V was not simple, but the technology transfer process was instructive. Russian scientists gave willing drug companies essential ingredients for the vaccine and lists of equipment and supplies, as well as visited the plants to teach and supervise the local staff.

Hemanth Nandigala, the managing director of one company producing Sputnik V, Virchow Biotech in Hyderabad, India, said that such "hand holding" made the technology transfer faster — about three months — although scaling production, passing regulatory clearances and commercialization has taken another five months (Maxmen, 2021).

In essence, a similar model could be applied during this interim, short-term period where no sufficient experience and infrastructure currently exist on the African continent to support independent vaccine manufacture. As there is an urgent need to increase vaccine supply in Africa, it is important not to wait until such fully functional system is established but to initiate vaccine production on the continent as soon as possible, with help of the vaccine manufacturers, regulatory agencies, e.g., PEI, EMA etc., and other stakeholders.

Such partnership, so called "twinning" could be very beneficial, and to our opinion- is indispensable to efficiently perform the tech and reg transfer. In the initial phase enhanced oversight of the manufacturing, quality assurance (QA) and quality control (QC) would need to be performed by skilled MAH staff. Nevertheless, to assure long-term sustainability it becomes critical that an in-depth, well documented, long-term training program is created for local staff in parallel.

Moreover, a regulatory oversight in this interim period would need to be performed by a mature agency such as e.g., PEI of Germany, too. This could be coupled with side-by-side oversight of the local NRA. Such approach should include a tutorship and guidance from experienced NRAs, which offers a valuable learning opportunity to the local regulatory experts, that might help in the long run establishing a new, mature vaccine regulatory system on the African continent.

Taken together, the technical and regulatory concepts proposed in the White Book aim at overcoming two major dilemmas. Taking African NRAs to competitive maturity levels alone is insufficient as access to technologies is required in parallel to achieve the goal of autonomy in vaccine production. On the other hand, access to contemporary technologies without a robust regulatory infrastructure is also unlikely to result in sustainable autonomy. Consequently, both streams need to be established and further developed in parallel as one approach is unlikely to work without the other. A way to reach both goals is to seek for a coordinated and generally accepted transfer of fully functional and licensed manufacturing units to African countries. Example of this approach to transfer technology could be by obtaining approval of EMA´s change management protocols or FDA´s comparability protocol (Post-approval Change Management Protocols, Comparability Protocols for Human Drugs and Biologics). These tools are available from EMA and FDA providing robust predictability of project implementation timelines and reduce business risks. This approach will ensure immediate onset of local vaccine production while strengthening the required regulatory framework required for sustainable control of vaccine production and release in parallel, according to WHO's rules and procedures as described in the chapters further above.

13. "Future prospect": Long-term goal

In addition to the tech- and reg- transfer and utilisation of already existing licensures that enables fast initiation of urgently needed SARS-CoV-2 vaccine production in Africa, an alternative and more sustainable approach should be developed **in parallel**.

Although transfer from highly developed regulatory regions of already qualified technologies offers an attractive, time-saving solution that seems most appropriate considering the current pandemic, it is providing only limited opportunity to create a sustainable regulatory framework for the African continent. The ultimate goal, however, should be to establish a robust, independent regulatory system that will allow efficient control and oversight of vaccine manufacturing in Africa.

Having such a mature, local vaccine regulatory system is critical as it is a prerequisite to achieving vaccine manufacturing independency and self- sustainability. As already described in this document, the export of locally manufactured vaccines via the WHO Prequalification procedure will require that the overseeing local NRA reaches at least Maturity Level 3 according to WHO's GBT.

Currently, two African NRAs reached Maturity Level 3:

- Tanzania (TMDA achieved ML3 in December 2018).
- Ghana (FDA achieved ML3 April 2020).

However, this currently still excludes vaccine manufacturing. Lack of an existing vaccine lot testing and release facility was given as the biggest obstacle to reach ML3 level for vaccine oversight in these countries, with South Africa currently the only country in Africa to have NCLs recognised by WHO. Nevertheless, it is important to point out that the majority of the African countries are currently at ML1 level. Many of these do not have an autonomous NRA, which means that the oversight and activities performed routinely by independent mature NRAs are in such cases fragmented and scattered across various departments, usually within the Ministry of Health (MoH).

Considering the abovementioned, there is no doubt that establishment of fully functional, independent NRAs in countries currently at ML1 or ML2 level will be a cumbersome and lengthy operation. Of course, such processes will require a lot of commitments from various stakeholders as well as substantial financial investments.

Moreover, the establishment of a multinational testing laboratory for Control Authority Batch Release of Vaccines could be envisioned, where experts from contributing countries are operating in a work-shared manner to reduce costs. This would establish a best-in-class excellence African Testing Centre for contributing countries. Overall, it has never been clearer that such efforts are crucial to safeguard the health of the African and global population. The current SARS-CoV-2 pandemic revealed that new solutions and incentives are needed to avoid future inequities in vaccine distributions. The stark contrast in vaccine coverage levels between high and LMIC demonstrates the urgent need for local and self-sustained vaccine manufacture. This translated into the establishment of multiple local and global alliances as well as in numerous multilateral political declarations aiming at addressing this protection divide.

As such, it is important to utilise the current incentives, political willingness, and economic investments to establish a system that can allow fast and streamlined creation of local regulatory systems, both at the country level (ML3 NRAs), as well as on a regional/continental level (AMA).

To achieve this, it is important to consider:

- Creation of such sustainable systems should be built upon the existing experience:

Firstly, the utilisation of incentives such as the one described in this White Book could prove very beneficial. For example, the operational as well as regulatory experiences gathered during the tech and reg transfer and production of SARS-CoV-2 vaccine in Africa, as described in Chapter 12, could help establishing processes and policies to be implemented in local systems. Moreover, the manufacture of pre-licensed vaccines locally in Africa requires building up essential infrastructures (incl. manufacturing facility), which could be subsequently used to produce other vaccines needed in the region.

As such, African countries that declared interest in manufacturing vaccines will continue gathering experience with vaccine manufacturing, QC, and regulatory oversight. In these first steps twinning projects with institutions from the so called "global north" are needed to gather solid vaccine manufacturing knowledgebase, that could be then exchanged with other African counties (twinning projects within the "global south"). Such experience-sharing might be very beneficial to other African countries as it will allow rapid assessment of the gaps and similarities between the countries considering the specifics of the respective geopolitical region (e.g., procurement, logistics, legislature).

- It should also reflect already existing legislation in the African countries of Interest and identify potential gaps in currently existing regulatory frameworks.

As mentioned above, currently no African country reached ML3 level required for vaccine production and export in accordance with WHO's Prequalification procedure.

As such potential gaps and deficiencies must be then reviewed with urgency considering already existing, ongoing and planned harmonisation incentives:

  - Model Law on Medical Products Regulation (2016) (link).
  - Pharmaceutical Manufacturing Plan for Africa (PMPA).

And using currently existing platforms/forums:

  - The African Vaccine Regulatory Forum (AVAREF) established 2006 by WHO (link).
  - The African Medicines Regulatory Harmonisation Initiative (AMRHI) established since 2009 as part of the AU PMPA.
  - The Pan-African Clinical Trials Registry (PACTR) established in 2012.
  - **The Partnerships for Vaccine Manufacturing (PAVM)** initiative created by African CDC in April 2021.

The creation of a mature and elaborated regulatory framework for vaccine manufacture should aim to harmonise local procedures with the ones existing in mature regulatory frameworks (e.g., of EMA, FDA) to deliver final products of high quality, not inferior to the ones licensed in

developed regulatory regions. With the Treaty for Establishment into force as of November 5th, 2021, such regulatory development should be embedded within the structures of the **African Medicines Agency (AMA)**.

Establishing a single centralised, high-quality regulatory authority is envisaged to provide tremendous benefits and greatly facilitate the development of such mature vaccine regulatory environment, as it was achieved with e.g., the EMA for the EU region. One of the most crucial advantages of such centralised assessment is sharing human resources and unique expertise, scarce- yet indispensable to perform the assessment of such complicated molecules and advanced technologies for better (quicker) access of African citizen to medicinal innovations. Next, avoidance of duplication of regulatory procedures within several countries allows to save time and resources, greatly speed up the entire process and gives much higher flexibility, resulting in better competitiveness relative to other regulatory regions, e.g., US, EU, Association of Southeast Asian Nations (ASEAN), Eurasian Economic Union (EAEU).

Furthermore, the coordinating role of AMA is of a particular importance in pandemic situations. Accelerated development under pandemic conditions requires lightening of regulatory burden for developers. Moreover, requirements for process changes and tech transfer are significantly higher to ensure supply chain and to react adequately to limited raw materials and manufacturing capacities. Hence, streamlining regulatory processes via AMA will ensure more rapid implementation of changes which can ensure adequate vaccine supply.

As such, it becomes highly important that the growing vaccine manufacturing experience will be utilised not only to strengthen national regulatory systems but is also to share across the continent when embedded within the structures and the mandate of the AMA.

14. Appendix: SARS-CoV-2 vaccines and beyond – General description of production platforms for vaccines

14.1 mRNA vaccine

14.1.1 Manufacturing of drug substance

The manufacturing process of mRNA vaccine drug substance (DS) involves five major steps. The RNA is manufactured by IVT using a linear DNA template, produced via plasmid DNA from transformed *Escherichia coli* cells. The linear DNA template is not part of the final product but defines the sequence of the mRNA product and therefore it is fundamental to ensure the adequate control of the active substance.

Following fermentation, the cells are harvested and chemically lysed to recover the plasmid DNA. After the lysis step, the circular plasmid DNA is purified. The circular plasmid DNA is filtered and stored frozen. All materials used are animal origin free and sourced from approved suppliers. Process- and product-related impurities including host cell genomic DNA, RNA, proteins, endotoxins, bioburden, and plasmid isoforms, for the plasmid DNA, are routinely quantified.

Two active substance processes have been used during the development; Process 1 and 2. The major changes between AS Process 1 and 2 are: increased process scale, DNA template changed from a polymerase chain reaction (PCR) template to linearised plasmid DNA, magnetic bead purification replaced with proteinase K digestion and Ultrafiltration/Diafiltration (UFDF) steps.

The active substance is stored between -15ºC and -25ºC. Transportation using an insulated shipper is qualified and shipping time to finished product manufacturing sites are defined.

14.1.2 Manufacturing of drug product

The manufacturing process includes lipid nanoparticle (LNP) fabrication and bulk finished product formulation followed by fill and finish. The finished product manufacturing process includes the following main steps: active substance thawing and dilution, LNP formation and stabilisation, buffer exchange, concentration and filtration, concentration adjustment and addition of cryoprotectant, sterile filtration, aseptic filling, visual inspection, labelling, freezing and storage. Relevant in-process controls are applied.

The finished product is supplied as preservative-free, 5 dose multidose concentrate to be diluted prior to intramuscular injection. The finished product is a sterile dispersion of RNA-containing lipid nanoparticles in aqueous cryoprotectant buffer.

The LNPs consist of four lipids, each has a functional or structural purpose. The formed RNA-containing LNPs are solid particles.

14.2 Recombinant protein vaccine

14.2.1 Manufacturing of drug substance

The DS is produced by creating an engineered baculovirus containing a gene for a modified SARS-CoV-2 spike protein. The DS then undergoes a series of sequential purification steps. The final steps include formulation and filtration using a bioburden reducing filter (0.22 µm). The DS is stored at ≤-60ºC.

14.2.2 Manufacturing of drug product

The DS is thawed, and then transferred to a mixing vessel for DP formulation. The formulated DP is then sterile filtered and filled into glass vials, which are stoppered and capped. After inspection, finished product is stored at 2-8ºC.

14.3 Viral vector vaccine

14.3.1 Viral vector vaccine #1

14.3.1.1 Manufacturing of drug substance

The manufacturing process is divided into cell culture and downstream processing. The cell culture consists of four steps: vial thaw, inoculum expansion in shake flasks and rocker bags, seeding of bioreactor(s) for further expansion of inoculum and production bioreactor to generate crude active substance.

The production bioreactor cell culture is lysed using detergent-based cell lysis, treated with nuclease for reduction of host cell DNA and then clarified via depth filtration. The clarified lysate is further processed through a membrane chromatography step designed to remove process-related impurities. This is followed by concentration and diafiltration using tangential flow ultrafiltration to remove process-related impurities and for buffer exchange. Next, a formulation step and a 0.2 µm filtration step into specified containers follows to generate the DS. The DS is frozen for storage (at -90ºC to -55ºC) and shipping.

14.3.1.2 Manufacturing of drug product

The frozen DS is shipped at -90ºC to -55ºC to the fill facility. Upon receipt, the DS is stored at -90°C to -55°C prior to processing. The DS is thawed, mixed, and pooled into a mixing vessel and dilution buffer is then added to the mixing vessel. Dilution buffer and DS is then mixed to produce final bulk. The final bulk is 0.45 µm (bioburden reduction) filtered into a holding bag prior to filling. During the filling process, the final bulk is 0.2 µm sterile filtered, using redundant sterile filters in series, as it is aseptically filled into sterile vials, closed with sterile stoppers, and sealed with aluminium caps. The resulting DP is 100% visually inspected, packaged and labelled on site.

14.3.2 Viral vector vaccine #2

14.3.2.1 Manufacturing of drug substance

The DS manufacturing process consists of ten stages: 1) pre-culture; 2) cell expansion; 3) virus production; 4) lysis; 5) DNA precipitation; 6) clarification; 7) anion-exchange chromatography (AEX); 8) polishing and buffer exchange; 9) final adjustment and fill, and finally 10) freezing of the DS.

The process starts with thawing of a vial of the cell substrate. Cells are expanded and then inoculated with the recombinant adenoviral construct. After virus production the cells are lysed, and virus is collected. Purification steps include a DNA precipitation step, a clarification, an anion-exchange chromatography step, and diafiltration. The diafiltered product is then formulated and undergoes a 0.2 µm filtration before filling in polycarbonate bottles. No reprocessing is claimed. The DS is stored below -40°C.

The manufacturing process is performed in a production facility at controlled room temperature.

14.3.2.2 Manufacturing of drug product

The DP manufacturing process consists of several steps. First, the DS is thawed, pre-filtered, pooled and diluted with pre-filtered formulation buffer. The formulated bulk is homogenised, sterile-filtered in-line (two 0.2 µm filters connected in series) and aseptically filled into vial, stoppered and capped. Filling is done immediately after sterile filtration. The sterile-filtered bulk is not stored. Subsequently, the vials are visually inspected, frozen, labelled and packaged.

14.4 Inactivated vaccine

14.4.1 Manufacturing of drug substance

Vero cells are used as substrate for the propagation of virus of interest. After virus inoculation and propagation, virus harvests are filtered, pooled, and concentrated. The concentrated virus pool is treated to remove Vero cell DNA. The virus pool is then purified. The purified virus material is inactivated with formaldehyde and then neutralised. Following neutralisation, the inactivated virus is sterile filtered through two 0.2 µm filters. The DS is processed immediately to final bulk vaccine/DP.

14.4.2 Manufacturing of drug product

Following adsorption of the DS onto adjuvant systems, the final bulk is stored until shipment to the filling plant. The final bulk DP is mixed continuously during the filling process.

15. Country specific appendices

15.1 Ghana

15.1.1 Ghana Food and Drugs Authority

The Food and Drugs Board (FDB) was established in August 1997 under the Food and Drugs Law, 1992 (PNDCL 305B). The Food and Drugs legislation was revised in 2012 and integrated into a new Public Health Act 851, 2012 that gave birth to the Food and Drugs Authority (FDA).

The FDA Ghana is the National Regulatory Authority mandated to regulate food, drugs, food supplements, herbal and homeopathic medicines, veterinary medicines, cosmetics, medical devices, household chemical substances, tobacco, and tobacco products. The FDA Ghana's legal mandate is found in Part 6 (Tobacco Control Measures), Part 7 (organisation and responsibilities of the FDA), and Part 8 (Clinical trials) of the Public Health Act, Act 851 of 2012. The FDA Ghana is an independent Agency under the Ministry of Health, which objective is to provide and enforce standards for the sale and to ensure the safety, quality, and efficacy of food, herbal medicinal products, cosmetics, drugs, medical devices, and household chemical substances.

The FDA Ghana was designated by the New Partnership for African Development (NEPAD) and the African Regulatory Harmonisation (AMRH) as a Regional Centre of Regulatory Excellence (RCORE) in Drug Registration in May 2014. As an RCORE, the FDA Ghana in collaboration with the School of Public Health, University of Ghana, seeks to build capacity in dossier assessment within the sub-region and improve access to medicine through harmonisation of regulatory requirements, which will ensure that quality, safe, and efficacious medicines are available to African citizens.

15.1.2 Structure of FDA Ghana

15.1.2.1 Governing body of the authority

The governing body of the Authority is an eleven-member Board, which is tasked to ensure the proper and effective performance of the functions of the Authority (Parliament of the Republic of Ghana, 2012).

The Board consists of:

- A chairperson.
- One representative of the Standards Authority.
- One medical practitioner who is a specialist in active practice nominated by the Minister of Health.
- One representative each of:
    - One pharmacist nominated by the Pharmacy Council.
    - The Centre for Scientific Research into Plant Medicine.
    - The Attorney-General not below the level of Principal State Attorney.
    - The Veterinary Services Department.
    - The Food Research Institute.
    - One traditional medicine practitioner nominated by the Traditional Medicine Practice Council.
- The Chief Executive Officer of the Authority.
- One other person who is a woman.

15.1.2.2 Management

Administratively, the FDA Ghana is headed by the Chief Executive Officer who reports directly to the Governing Board. The Chief Executive Officer of the FDA Ghana takes responsibility for the daily operational management, service delivery and strategic issues of the FDA Ghana.

The office of the Chief Executive consists of:

- Internal Audit.
- Human Resource.
- Communications and Public Education.
- Project, Research, and Management Information Systems.
- Finance.
- Administration.
- Import and Export Control.
- Laboratory Services Departments and Regional Offices.

15.1.2.3 Technical Advisory Committees

The Technical Advisory Committees (TAC) for Safety was formed to act as a forum to advice the FDA Ghana on matters relating to the post-approval safety, quality, efficacy, and effectiveness of products granted Marketing Authorisation by the Authority (FDA Ghana: Corporate Profile). The committees are made up of experts from different scientific backgrounds (FDA Ghana: Technical Advisory Committees).

The FDA Ghana has five TACs:

- TAC for safety of medicines.
- **TAC for safety of vaccines and biological products.**
- TAC for medical devices.
- TAC for clinical trials.
- TAC for nutrition.

The main role of TACs is to provide expertise to assist the FDA Ghana in making appropriate risk management decisions, as well as to provide an ongoing and timely medical and scientific advice on current and emerging issues related to post-approval product surveillance based on spontaneous reports received from healthcare professionals and decisions taken by National Regulatory Authorities (NRAs) worldwide. Nevertheless, it is important to highlight that the role of TAC is auxiliary, and the decision-making responsibility remains with the FDA Ghana.

15.1.2.4 Divisions of FDA Ghana

Under the Chief Executive there are five Specialised Divisions, namely (FDA Ghana: Management Structure):

- Food Division,
- **Drug Registration and Inspectorate Division**,
- Safety Monitoring and Clinical Trials Division,
- Cosmetics, Medical Devices, and
- Household Chemicals Division, and Monitoring and Evaluation Division.

In this White Book, only divisions and/or departments which are deemed to be relevant for the regulatory and technology transfer and establishment of sustainable vaccine production in Ghana are described. As such, the focus will be on the Drug Registration and Inspectorate Division and its subordinate departments (FDA Ghana: Drug Registration and Inspectorate Division).

15.1.2.4.1 Drug Registration and Inspectorate Division

The Division's mandate as derived from Parts 6, 7 & 8 of the Public Health Act 2012, Act 851, is to protect public health and safety by ensuring the availability of safe, efficacious, and quality allopathic medicines, veterinary medicines, **vaccines**, biological products, tobacco & tobacco products, herbal medicines, homeopathic medicines, food supplements, medical devices, cosmetics, and household chemical substances on the Ghanaian market.

Under the Drug Registration and Inspectorate Division are:

1. Clinical Trial Department.
2. Drug and Nutraceuticals Department.
3. Herbal and Homeopathic Medicines Department.
4. **Vaccines and Biological Products Department.**
5. Tobacco and Substances of Abuse Department.
6. Medical Devices Department.
7. Cosmetics and Household Chemicals Substances Department.
8. Safety Monitoring Department.

AD.1: Clinical Trials Department

The Clinical Trials Department of the FDA Ghana is responsible for authorisation and monitoring of clinical trials as required by Part 8 of the Public Health Act, 2012 Act 851. The legal mandate of the FDA Ghana as per Part 8 of the Public Health Act 2012, Act 851 is to authorise and monitor clinical trials through:

- Development of appropriate guidelines for the conduct of clinical trials.
- Issuance of Clinical Trial (CT) Certificates (permit for conducting clinical trials).
- Reviewing of all reports from trial site.
- Conducting Good Clinical Practice (GCP) inspections at trials sites to ensure compliance of trials to international best practices and local regulatory requirements.
- Investigating the conduct of clinical trial.
- Suspension or stopping clinical trials (if necessary).

Currently the Department has two (2) units with the following activities:

- Clinical Trials Authorisation Unit:
    - Receiving of Clinical Trial Applications (CTAs).
    - Planning, scheduling, and coordinating of CTA evaluation meetings.
    - Evaluation of CTAs and amendments.
    - Correspondence of evaluation on CTAs and amendments to applicants.
    - Processing of permits for Investigational Products.
    - Acknowledgement of general correspondences.
    - Coordinating and planning of TAC meetings.
    - Developing and updating relevant information on the FDA website.
- Clinical Trials Compliance Unit:
    - Update and maintenance of data on approved clinical trials.
    - Receipt, evaluation, and acknowledgement of Serious Adverse Event (SAE) reports.
    - Processing SAEs for TAC meetings.
    - Planning and coordinating GCP inspections for ongoing studies.
    - Conducting GCP inspections at trial sites of ongoing studies.
    - Organising GCP trainings for Research Institutions.
    - Coordinating training workshops (Internal & External).
    - Receipt and review clinical trial reports (quarterly and final).

Operational Guidelines and Tools

The Clinical Trials Department in carrying out its mandate and daily activities has developed the underlisted tools, which are periodically reviewed and updated to ensure compliance with international best practices. The FDA Ghana has also adopted for use, the **Africa Vaccine Regulatory Forum (AVAREF)** forms, checklists, and guidelines on Clinical Trials.

- Four (4) guidelines:
  - **Guidelines for Authorization of Clinical Trials of Medicines, Food Supplements, Vaccines and Medical Devices in Ghana.**
  - Guidelines for GCP in Ghana.
  - Guidelines for Conduct of Clinical Trials in Paediatric Population.
  - Guidelines for Conduct of Clinical Trials During Emergencies.
- Standard Operating Procedures (SOPs) for carrying out all departmental activities.
- Clinical Trial Application Form (completed and submitted together with other documents during a clinical trial application submission).
- Quarterly Progress Report Form (trial sites report progress of approved ongoing trials quarterly).
- Clinical Trial Close-out Report Form (submitted by trial when trial ends and close-out activities have been carried out).
- Clinical Trial Report Form (format used in reporting final trial reports at the end of trials, that is ICH E3).

Achievements

- Designation of the FDA, Clinical Trials Department as a RCORE in clinical trials by AUDA-NEPAD since 2014. The FDA as an RCORE in clinical trials has trained 54 regulators in Sub-Saharan Africa in order to enhance capacity of regulators in the field of clinical trials.
- Member of African Vaccine Regulatory Forum (AVAREF) since 2006 till date. This has contributed to harmonisation of regulatory procedures across Africa.
- First country to participate in registration of clinical trials on AVAREF adopted site Pan-African Clinical Trials Registry (PACTR).
- Representation on the Ministry of Health's Ethics Committee (the largest for public health trials).
- Non-EU member of European Medicines Agency (EMA) GCP Inspectors' Working Group.

AD.2. Drug and Nutraceuticals Department

The Mandate of the Drug and Nutraceuticals Department is defined by the following Sections of Part 7 of the Public Health Act, 2012, Act 851:

- Section 117 Application for Registration.
- Section 118 Registration of Drugs.
- Section 119 Cancellation or Suspension of Registration.
- Section 147 (1)-(3) Regulations.
- Section 148 (1)-(4) Guidelines and Codes of Practice.

Scope of Mandate

The Department processes and grants market authorisation for allopathic medicines (human and veterinary) intended for export and/or sale on the Ghanaian market.

Operational Activities

The operational activities of the Department are as follows:

- Processing approvals for new, renewal, and variation applications.
- Coordinating dossier evaluation and product registration meetings.
- Maintaining the Drug Register.
- Correspondence with applicants.
- Issuance of registration certificates.
- Revocation of registration certificates.
- Drafting and reviewing of guidelines and codes of practice.
- Stakeholders´ engagement on matters relating to registration of pharmaceutical products.

The Department has three operational units, which are:

- The Local Medicines Registration Unit.
- The Fast-Track/Low-Risk Registration Unit.
- The Foreign High-Risk Registration Unit.

AD.3. Herbal and Homeopathic Medicines Department

The Mandate of the Herbal and Homeopathic Medicines (HHM) Department is defined by the following Sections of Part 7 of the Public Health Act, 2012, Act 851:

- Section 117 Application for Registration.
- Section 118 Registration of Herbal Medicinal Products.
- Section 119 Cancellation or Suspension of Registration.
- Section 124 Registration of Homeopathic Drug.
- Section 128 Herbal Medicinal Products and Homeopathic Drug Register.
- Section 147 (1)-(3) Regulations.
- Section 148 (1)-(4) Guidelines and Codes of Practice.

Scope of Mandate

The Department processes and grants market authorisation for herbal and homeopathic medicines intended for export and/or sale on the Ghanaian market.

Operational Activities

The operational activities of the Department are as follows:

- Processing and approvals for new, renewal and variation applications.
- Coordinating dossier evaluation and product registration meetings.
- Maintaining the herbal and homeopathic medicines register.

- Correspondence with applicants.
- Issuance of registration certificates.
- Revocation of registration certificates.
- Drafting and review of guidelines and codes of practice.
- Stakeholders´ engagement on matters relating to registration of pharmaceutical products.

The Department has two operational units:

- The Herbal and Homeopathic Medicines Unit.
- The Food Supplements of Herbal origin Unit.

AD.4. Vaccine and Biological Products Department

The mandate of the Vaccines and Biological Products Department (VBPD) is to apply appropriate regulatory instruments, including guidelines and policies to ensure that only **Quality, Safe, and Efficacious Vaccines and Biological Products are approved to be imported and used in Ghana.**

VBPD manages and coordinates the evaluation processes, which precedes the granting of Marketing Authorisation (MA). In addition, VBPD conducts audits of Blood Facilities towards their licensure and listing of Blood and Blood Components (BBC) prepared by the facility to ensure blood safety nationwide.

Currently, the Department operates with three distinct units. These are:

- **Vaccine and Advance Therapy Medicinal Products Unit.**
- **Biotechnology-Derived Medicinal Products Unit.**
- Blood and Plasma-Derived Medicinal Products Unit.

AD.5. Tobacco and Substances of Abuse Department (TSAD)

The mandate of the Tobacco and Substance of Abuse Department is defined by Part 7-Section 126 and Part 6 of the Public Health Act, 2012, Act 851 and the Tobacco Control Regulations, 2016 (LI. 2247).

Scope of Mandate

Department operations cover the utilisation of narcotic drugs, psychotropic substances, and chemical precursors for medical, scientific and research purposes only, whilst preventing its abuse and diversion from licit to illicit use. The Department is also responsible for the regulation of tobacco and tobacco products to ensure reduction and subsequent prevention of tobacco use through effective implementation of the tobacco control measures.

Operational Activities

The operational activities for the Department are as follows:

- Public education on the abuse of substances and tobacco and tobacco products.
- Development of information and educational communication materials to promote and create awareness associated with tobacco use and substance abuse.

- Allocation of controlled substances to importers.
- Issuance of permits for controlled substances, raw material, and finished products.
- Monitoring of controlled substances to prevent its diversion to illicit use.
- Correspondences with the International Narcotics Control Board.
- Stakeholder's engagement activities including the celebration of international days such as World No Tobacco Day, International Drug Day.
- Registration and issuance of certificates for tobacco and tobacco products.
- Maintain the tobacco register.
- Registration of importers of tobacco and tobacco products.
- Monitoring compliance to tobacco control regulations.
- Dossier evaluation.
- Drafting and reviewing of guidelines.

The Department has two operational units:

- The Narcotics Unit.
- The Tobacco Unit.

AD.6. Medical Devices Department

The mandate of the Medical Devices Department (MDD) is defined by the following Sections of Part 7 of the Public Health Act, 2012, Act 851:

- Section 118 Registration Medical Devices.
- Section 119 Cancellation or Suspension of Registration.
- Section 147 (1) - (3) Regulations.
- Part 7 Section 148 (1)-(4) Guidelines and Codes of Practice.

Scope of Mandate

The Department processes and grants market authorisation for medical devices intended for export and/or sale on the Ghanaian market.

Operational Activities

The operational activities of the Department are as follows:

- Processing approvals for new, renewal and variation applications.
- Participation in product registration meetings.
- Dossier evaluation.
- Maintain the medical devices register.
- Correspondence with applicants.
- Issuance of registration certificates.
- Revocation of registration certificates.
- Coordination of TAC Meetings on medical devices.
- Coordination of site testing of medical devices.
- Listing of importers of medical devices.
- Drafting and reviewing of guidelines and codes of practice.
- Stakeholders’ engagement on matters relating to registration of Medical Devices.

- Collaboration with Ghana Standards Authority (GSA) for the development of standards for medical devices.
- Collaboration with Nuclear Regulatory Authority for the regulation of radiation emitting medical devices.

The Department has two operational units:

- The Evaluation and Registration of Low-Risk Medical Devices Unit.
- The Evaluation and Registration of High-Risk Medical Devices Unit.

AD.7. Cosmetics and Household Chemical Substances Department

The mandate of the Cosmetics and Household Chemical Substances Department (CHCD) is defined by the following Sections of Part 7 of the Public Health Act, 2012, Act 851:

- Section 118 Registration of Cosmetics and Household Chemical Substances.
- Section 119 Cancellation or Suspension of Registration.
- Section 147 (1) - (3) Regulations.
- Part 7 Section 148 (1)-(4) Guidelines and Codes of Practice.

Scope of Mandate

The Department processes and grants market authorisation for cosmetics and household chemical substances intended for export and/or sale on the Ghanaian market.

Operational Activities

The operational activities for the Department are as follows:

- Processing approvals for new, renewal and variation applications.
- Participation in product registration meetings.
- Maintain the cosmetics and household chemical substances registers.
- Correspondence with applicants.
- Issuance of registration certificates.
- Revocation of registration certificates.
- Registration of importers of cosmetics and household chemical substances.
- Drafting and review of guidelines and codes of practice.

The Department has two operational units:

- The Cosmetics Unit.
- The Household Chemical Substances Unit.

AD.8. Safety Monitoring Department

The mandate of the Safety Monitoring Department (SMD) is defined in Section 125 of the Public Health Act, 2012. The Department hosts the National Pharmacovigilance Centre. The Centre joined the **WHO Programme for International Drug Monitoring (PIDM)** in November 2001 as the 65th member of the Programme.

The safety monitoring system in Ghana is decentralised to ensure efficient and effective coordination of pharmacovigilance activities in all 16 regions.

There are Institutional Contact Persons (ICPs) at the healthcare facilities with responsibility for safety monitoring of drugs, **vaccines,** and other health products. The ICPs act as the point of contact for the FDA with regard to the safety monitoring of products within the health facilities.

The SMD has two units:

- The Vigilance Unit.
- The Risk Management Unit.

Vigilance Unit

- Ensure pharmaceutical industries comply with the safety monitoring requirements.
- Carry out Good Pharmacovigilance Practice Inspections.
- Liaise with Public Health Programmes to ensure pharmacovigilance becomes an integral component of these programmes.
- Create awareness on pharmacovigilance for healthcare professionals and to the general public.
- Organise training programmes for stakeholders.
- Produce Drug Safety Newsletter (DrugLens) and Patient Safety Newsletter.
- Produce Information Education and Communication materials to promote safety monitoring of products.

Risk Management Unit

- Ensure availability of reporting forms at user points and functioning of the electronic platforms for reporting adverse events.
- Maintain the FDA's Safety Database (Safety Watch System).
- Receive and process individual Case Safety Reports.
- Coordinate TACs meetings.
- Communicate alerts and safety issues to stakeholders.
- Review safety information including but not limited to Risk Management Plans (RMPs) and Periodic Safety Update Reports/Periodic Benefit-Risk Evaluation Reports and Safety variations for regulated products submitted to the Authority.
- Follow up on the implementation of risk minimization activities.
- Ensure the Department's commitment to the FDA's quality management system.

In 2016, the FDA embarked on an initiative to empower the consumers and patients to report safety issues of regulated products to the FDA through Community Pharmacies designated as Patient Safety Centres.

Moreover, the Med Safety App was introduced in 2019 as an additional reporting tool to ensure real time reporting of safety issues for medicines, vaccines, and other related health products.

Furthermore, the SMD has several years of experience in monitoring the safety of vaccines. The Department effectively coordinated the introduction of new vaccines including the pneumococcal/rotavirus vaccines, measles rubella, and the ongoing Malaria Vaccine Pilot Implementation Programme, which has been going on for close to two years without major safety concerns.

Lastly, the SMD is also a RCORE and serves as a training centre for regulatory from other African Countries.

Collaborating Agencies and Stakeholders

- Medicines and Healthcare Regulatory Agency (MHRA): Technical assistance with the development of consumer/patient reporting system for reporting safety issues and E2B compliance database (Safety Watch System) for safety data management.
- WHO/ Uppsala Monitoring Centre: Technical assistance in the form of training.
- Ghana Health Service (GHS): Monitoring and evaluation of Pharmacovigilance performance within healthcare facilities using the pharmacovigilance assessment tool.

Other Agencies the Department collaborates with are:

- USAID (United States Agency for International Development) through the Strengthening Health Outcomes through the Private Sector.
- West African Health Organization.
- African Collaborating Centre for Pharmacovigilance.
- Public Health Programmes (PHPs).

PHPs involve the administration of medicines to large populations. Pharmacovigilance plays a role in the successful implementation of PHPs. In view of this, the SMD coordinates pharmacovigilance activities in collaboration with the underlisted PHPs.

- **Expanded Programme on Immunization (EPI):** Coordinates adverse event following immunization (AEFI) monitoring during vaccination campaigns and routine immunization programmes. The Department ensures that the reports were evaluated by the Technical Advisory Committee on Safety of Vaccines and Biological Provides (TAC-VBP) and feedback provided to the EPI and other stakeholders.
- National Malaria Control Programme (NMCP): Coordinates the monitoring of adverse events in the Seasonal Malaria Chemoprevention and other anti-malaria campaigns.
- National Tuberculosis Control Programme (NTBCP): coordinates the monitoring of adverse events in patients on anti-tuberculosis medicines.
- National AIDS Control Programme: coordinates the monitoring of adverse events in patients receiving anti-retroviral therapy.
- Neglected Tropical Diseases Control Programme: coordinates the monitoring of adverse events in the patients receiving therapy for neglected tropical diseases such as Lymphatic Filariasis, Onchocerciasis, Trachoma, Schistosomiasis, Soil transmitted helminthiasis, Buruli ulcer, Yaws, Leprosy, Guinea worm, Human African Trypanosomiasis (HAT), Cutaneous Leishmaniasis and Rabies.

15.1.3 Current status of FDA Ghana

The benchmarking of the national regulatory system of Ghana was conducted by WHO Regulatory Systems Strengthening (RSS) Team in the area of regulation of medicines and vaccines from 25 to 29 March 2019 in collaboration with the WHO Regional Office for Africa and the WHO Country Office in Ghana (WHO, 2020). The benchmarking is part of the WHO programme for regulatory system strengthening and builds upon previous assessments conducted between 2013 and 2015, as well as WHO capacity building activities organised for FDA Ghana over the years (WHO, 2020).

During the follow up visit to FDA Ghana from 11 to 12 February 2020 and subsequent virtual meetings in March and April 2020, the WHO RSS team confirmed that FDA Ghana had implemented all recommendations and met indicators that define a Maturity Level 3 (ML3) regulatory system on a scale of one to four (WHO, 2020).

In addition, the SMD of FDA Ghana attained Maturity Level 4 (ML4) regulatory function by the WHO; the highest level any regulatory function can attain. This signifies the safety monitoring function of the FDA is at an advanced level of performance with continuous improvement needed in monitoring the safety of medicines, vaccines, and other health products (FDA Ghana: Safety Monitoring and Clinical Trial Division).

15.1.4 Preparedness of FDA Ghana for sustainable vaccine manufacturing

There are four levels of regulatory systems´ maturity starting from Level 1, where only some elements of regulation exist, and up to four corresponding to the advanced regulatory system, Level 3 indicates that the system is well functioning and integrates all required elements to guarantee its stable performance.

FDA Ghana achieved ML3 that took effect from 15 April 2020. With support of WHO and other partners, FDA Ghana strengthened its expertise, streamlined processes, and resources up to ML3 by WHO classification by implementing all critical recommendations from GBT.

However, it is important to state that currently FDA Ghana is classified ML3 for medicines and vaccines (non-producing). A robust regulatory system that allows efficient control and oversight of vaccine manufacturing is prerequisite to maintain an independent and sustainable local vaccine manufacturing sector. In addition, a comprehensive regulatory oversight is required for the vaccine manufactured to be eligible for WHO Prequalification and hence to be exported to other countries.

In summary, currently no vaccine manufacture takes place in Ghana and the Ghana FDA is not equipped yet to perform full regulatory oversight of the local vaccine production. Therefore, it becomes imperative for FDA Ghana to pursue ML3 for vaccines (producing). As the Agency is already performing regulatory oversight of other medicines, the expertise, at least to some extent, is already available in-house. Following diligent analysis, the remaining gaps, specifically regarding vaccine-specific regulation aspects should be closed as soon as possible, with help of individual specialists or other Agencies experienced in vaccine oversight via twinning partnership.

Also, one of the most critical aspects is the existence of well-equipped National Control Laboratory (NCL) that will allow oversight of the vaccine release activities. As the establishment of such NCL might be a time-consuming process, it is critical to initiate these efforts as soon as possible.

It is important to highlight that Ghana has a very robust and well-functioning regulatory system, as recognised by WHO and other international institutions. The vast network of collaborators, existing twinning programs and participation in multiple cross-continent initiatives position the Agency as a pioneering centre within the region. The existence of independent, well-organised Agency should play a key role in accelerating the process of readiness to effectively control not only the import of the vaccines, their implementation, and post-marketing activities (pharmacovigilance) but also to perform the regulatory oversight of the vaccine manufacture and release.

15.2 Rwanda

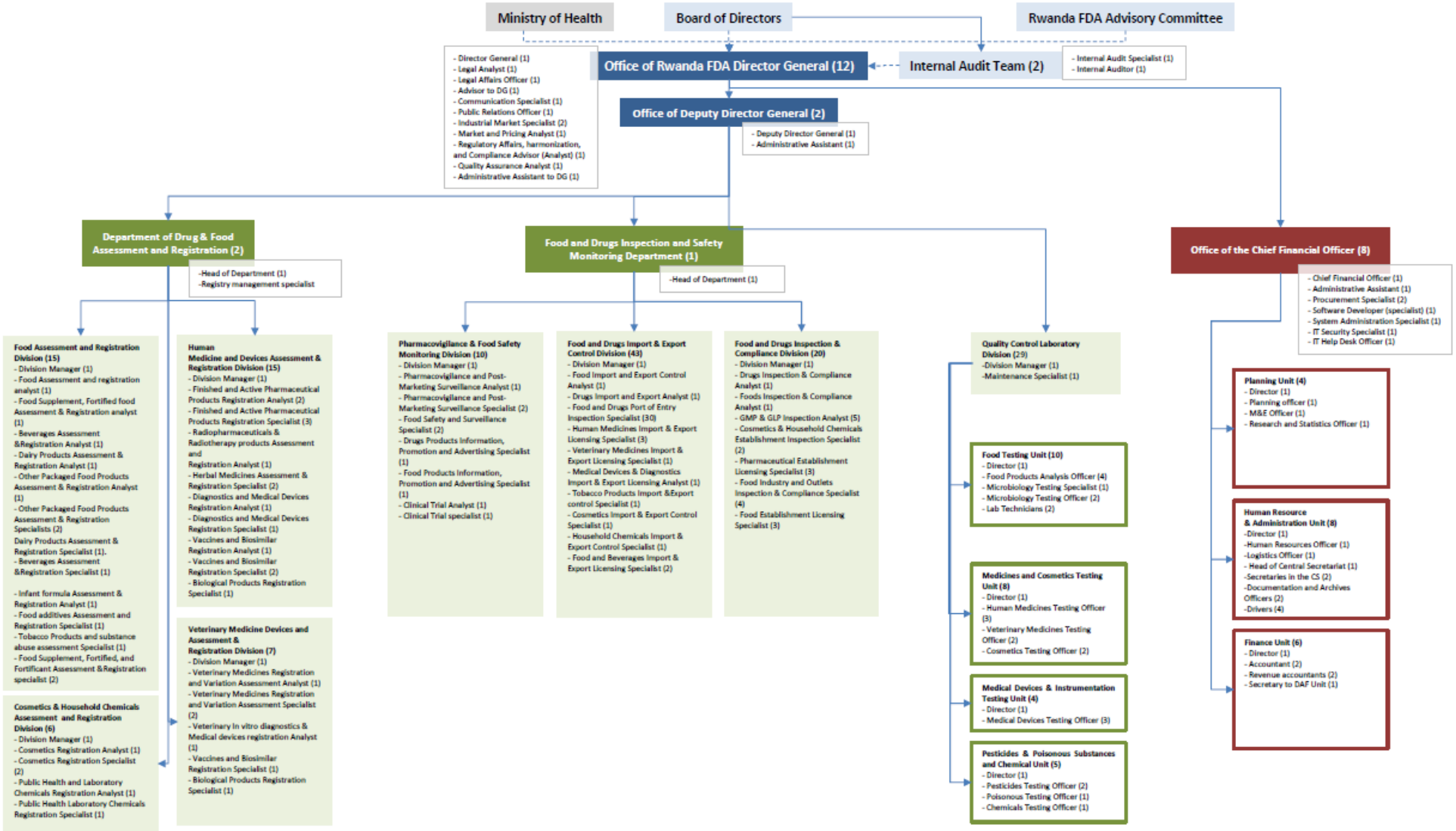
15.2.1 Rwanda Food and Drugs Authority

The Rwanda Food and Drugs Authority was established by the law No 003/2018 of February 9th, 2018 determining its mission, organisation and functioning (Rwanda FDA, 2020). Prior to its establishment, there was insufficient infrastructure and human resources to implement and operate an autonomous regulatory institution for both foods and pharmaceuticals.

The mandate of the Rwanda FDA is to protect public health through regulation of human and veterinary medicines, vaccines and other biological products, processed foods, poisons, medicated cosmetics, medical devices, household chemical substances, tobacco, and tobacco products (Rwanda FDA, 2020).

Rwanda FDA is a regulatory entity managed by the Director General who reports to the Board of Directors (BoDs) and it coordinates with line ministry responsible for health (Figure 5). The management organs of Rwanda FDA are the BoDs and Executive Organ. The BoDs of Rwanda FDA is the supreme management and decision-making organ, with full powers to make decisions regarding administration, human resources, and property of Rwanda FDA to fulfil its mission. The Executive Organ of Rwanda FDA has the responsibilities to monitor and coordinate daily duties and activities; to perform any other duty as may be assigned by the BoDs falling within the mission of Rwanda FDA. The Director General of Rwanda FDA has the power of decision in the administrative and financial management of Rwanda FDA in accordance with relevant laws (Rwanda FDA, 2021).

Figure 5: Organisational structure of Rwanda Food and Drugs Authority (Rwanda FDA, 2021)



Rwanda FDA functions are executed through three departments:

- The Food and Drugs Assessment and Registration Department (FDAR).
- The Food and Drugs Inspection and Safety Monitoring Department (FDISM).
- The Finance and Administration Department.

The three departments are further supported by eight divisions:

- Human Medicine and Devices Assessment and Registration.
- Cosmetics and Household Chemicals Assessment and Registration.
- Veterinary Medicine Devices and Assessment and Registration.
- Food Assessment and Registration.
- Drugs, Food Inspections and Compliance.
- Pharmacovigilance and Food Safety Monitoring.
- Food and Drugs Import and Export Control Division.
- Quality Control Laboratory.

15.2.2 Current status of Rwanda FDA

The first benchmarking activity was conducted in 2018 with assistance from WHO to assess the maturity level of the regulatory institution using the GBT. At the end of the assessment, 136 recommendations were identified in an IDP to improve the institution from maturity level 1 to maturity level 3 (Rwanda FDA, 2021). Table 3 summarises the findings of the assessment by regulatory function.

Significant room for improvement was identified in the areas of arrangement for effective organisation and good governance (50%), human resources to perform regulatory activities (50%); mechanisms to promote transparency, accountability, and communication (50%); legal provisions, regulations and guidelines required to define the regulatory framework (45%); and a quality management system (QMS) that includes risk management principles (29%) (Rwanda FDA, 2021).

Table 3: GBT findings by regulatory function (Adopted from Rwanda FDA Strategic Plan 2021-2024 (Rwanda FDA, 2021))

Regulatory Function	Components in Place	Areas for Improvement
National Regulatory Systems	• Rwanda FDA law approved and published in the country´s official gazette. • Developed organisational chart forming the basis for the operationalisation of Rwanda FDA. • Authority´s SP with objectives and a roadmap for its implementation is in its final development stage. • Financial needs and cost of operationalisation of Rwanda FDA have been clearly identified. • Many GBT sub-indicators can be fully implemented within few months.	• Despite leadership commitment for QMS implementation and becoming ISO 9001:2015 certified, the Authority is in need of a QMS, including risk management principles. • Significant room for improvement was identified in the areas of arrangement for effective organisation and good governance (50% of sub-indicators implemented); human resources to perform regulatory activities (50% of sub-indicators implemented); and mechanisms to promote transparency, accountability, and communication (50% of sub-indicators implemented).
Registration and Marketing Authorisation	• Most legal provisions in place. • Open-ended pre-registration status was issued to products once without a validity period. • Currently issuing finite registration license certificates. • Submission of dossiers in CTD format. • Reliance: EAC joint review outcomes are applied locally, occasionally relying on the Swissmedic procedure for MA for global health products.	• Guidelines yet to be developed include registration of products in emergency situations, timelines for processing of MA applications and related tracking system, and reliance on the MA decision of other national medicines regulatory authorities/international organisations. • Human resource constraints hampering the effectiveness of activities.
Vigilance	• PV centre with legal mandate to carry out its functions under the Rwanda FDA´s law. • Developed guidelines pending approval. • Regulations and SOPs in place.	• Designated staff to carry out PV activities. • Implementation of national database for collating ADRs. • Establishment of advisory committee to advise on causality assessment. • Development of communication strategy. • Low submission of ADR reports to the Uppsala Monitoring Centre (e.g., no reports were received at the centre in 2018, and 30 reports have been submitted to the centre´s database since 2012). • Stakeholder engagement in PV activities, particularly with public health programmes (e.g., HIV, TB, malaria, vaccines).
Market Surveillance and Control	• Legal framework and provisions drafted (i.e., regulations, guidelines, SOPs) but awaiting approval for implementation. • Human resource documentation developed (i.e., job descriptions with expected experience and qualifications, training plan).	• Need for guiding documents that facilitate transparency and communication of the market surveillance outcomes to the public. • Required staff to perform market surveillance and control activities not yet recruited.

Regulatory Function	Components in Place	Areas for Improvement
	• Required procedures to perform market surveillance and control activities (e.g., SOPs, risk-based post-marketing surveillance programme guidelines) drafted but awaiting approval.	
Licensing Establishments	• Application requirements (i.e., forms, checklists, guidelines, any administrative information) developed and implemented. • QMS to standardise operations developed and in place.	• Required staff not yet recruited; training plan yet to be developed. • Guidelines yet to be developed or approved (e.g., guidelines for inspection and licensing of premises, regulations on the variation of premises).
Regulatory Inspection	• Legal provisions developed and publicly available. • Centralised document control system enabling standardisation and control of documents produced by the Authority is in place.	• Required staff not yet recruited. • Training of personnel and qualification evaluation of the effectiveness of training should be prioritised. • Most regulatory inspection operations performed are not documented, especially procedures or documentation to show implementation of enforcement activities (e.g., investigations into quality issues) were not available.
Laboratory Testing	• Food laboratory, medical devices, veterinary medicines, and household chemical products testing is planned to be established. • Availability of adequate and well-maintained facilities for performing the testing. • QMS is in place according to ISO 17025. • Competent and motivated staff.	• Additional appropriately trained staff are needed for the development of microbiological testing. • Need for regulation describing the mechanism of QC of medicines, including the official issuance of laboratory testing results. • Memorandum of understanding defining the process of recognition of and reliance on the results of other laboratories needs to be enforced. • MA information needs to be made available to laboratory staff to ensure that testing is in accordance with the manufacturer´s methods. • Guidance on nonconformities and how to communicate with MA holders and other interested parties needs to be provided.
Clinical Trials Oversight	• Law mandating the Authority to regulate clinical trials in the country is in place. • Clinical trials oversight currently undertaken by the Rwanda National Ethics Committee.	• Drafted legal provisions need to be revised in accordance with the provisions of Law No 003/2018 of February 9, 2018. • Rwanda FDA is not involved in the regulation of clinical trials except for the issuance of a license for importation of medical products for clinical trials. • Limited number of human resources to carry out clinical trial oversight activities.

Abbreviations: ADR= Adverse Drug Reaction, CTD= Common Technical Document, EAC= East Africa Community, FDA= Food and Drugs Authority, GBT= Global Benchmarking Tool, HIV= Human Immunodeficiency Virus, MA= Marketing Authorisation, PV= Pharmacovigilance, QC= Quality Control, QMS= Quality Management System, SOP= Standard Operating Procedure, SP= Strategic Plan, TB= Tuberculosis.

15.1.3 The need for ML3 NRA

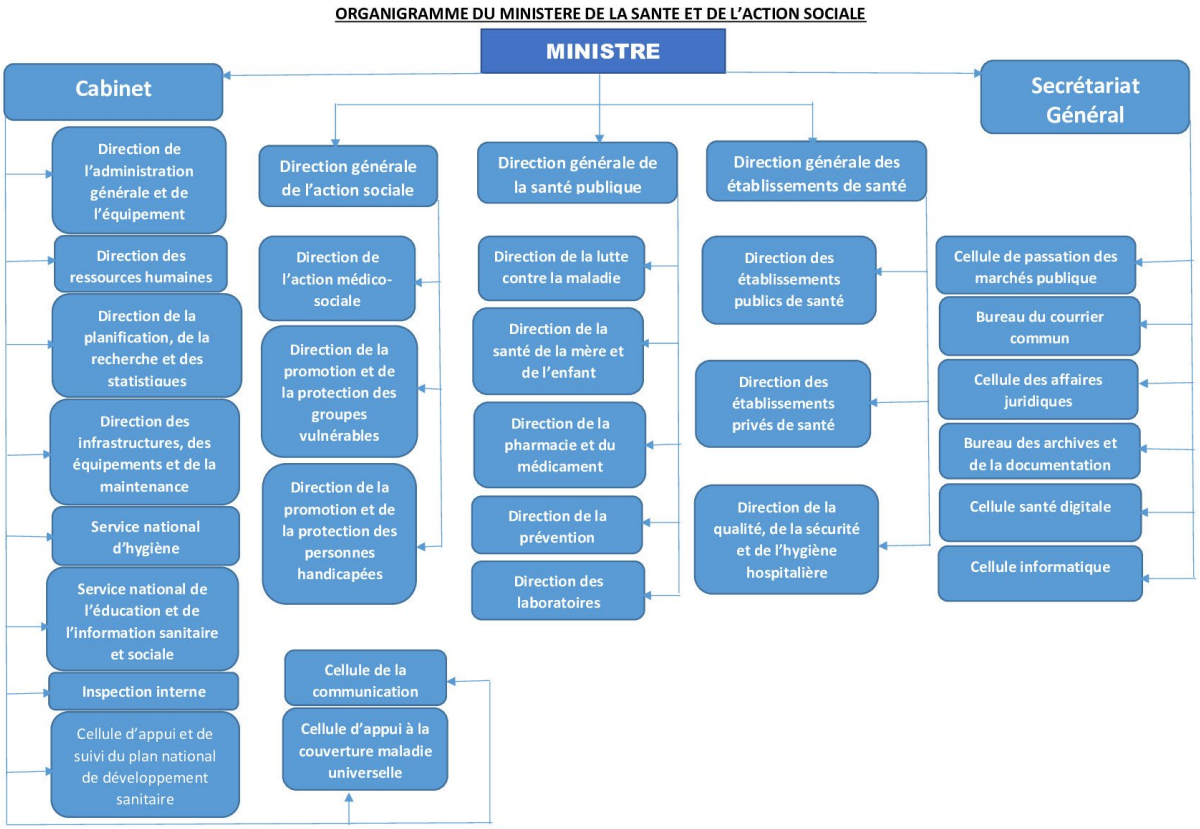
Since the establishment of Rwanda FDA in 2018, there has been significant improvement in the infrastructure and human resources to implement and operate an autonomous regulatory institution for medicinal products. However, as described in the previous section, significant improvement is required to transition from current ML1 to ML3 regulatory authority. A robust, independent regulatory system that allows efficient control and oversight of vaccine manufacturing is prerequisite to maintain an independent and sustainable local vaccine manufacturing sector.

In addition, although transfer of technologies qualified by other highly developed regulatory authorities provides time-saving alternative that is appropriate in the current pandemic, without comprehensive regulatory oversight, the vaccine manufactured in this facility will not be eligible for WHO Prequalification and hence unable to be exported to other countries. As such, it is imperative for Rwanda FDA to follow through the Rwanda Food and Drugs Authority Strategic Plan 2021-2024 to reach ML3 as soon as possible.

15.3 Senegal

Currently, Senegal does not have an independent NRA that allows efficient control and oversight of vaccine manufacturing locally. The MoH is the institution currently performing the tasks, which are usually the responsibility of NRA. The organisational structure of the MoH of the Republic of Senegal is presented in Figure 6.

Figure 6: Organisational structure of the Ministry of Health of the Republic of Senegal (Reprinted from the website of the Ministry of Health)



15.3.1 The need for ML3 NRA

As for the case in Rwanda, a robust, independent regulatory system that allows efficient control and oversight of vaccine manufacturing is prerequisite to maintain an independent and sustainable local vaccine manufacturing sector in Senegal.

In addition, although transfer of technologies qualified by other highly developed regulatory authorities provides time-saving alternative that is appropriate in the current pandemic, without comprehensive regulatory oversight, the vaccine manufactured in this facility will not be eligible for WHO Prequalification and hence unable to be exported to other countries. As such, it is imperative for Senegal to develop an independent and comprehensive regulatory system in collaboration with WHO and other international partners.

In January 2016, the AU Model Law on Medical Products Regulation, developed by African Union Development Agency New Partnership for Africa´s Development (AUDA-NEPAD), was officially endorsed (Ncube et al., 2021). The Model Law provides the legislative framework for

harmonisation at the regional and sub-regional level (Ncube et al., 2021). Furthermore, the Model Law could increase efficiencies in regional, sub-regional and national procedures (Ncube et al., 2021). Domestication and implementation of this legislation by Senegal for regulatory systems harmonisation will facilitate collaboration across countries and ensure that in countries involved in R&D medical products that hold promise will be developed, tested, and scaled up for the improvement of health impact.

AMA is mandated to coordinate the regional harmonisation systems that are enabled by AU Model Law domestication and implementation. As AMA officially came into force in November 5th, 2021, the establishment of an autonomous NRA according to the Model Law should become a priority. In the long term, this will allow further collaboration among African Member States that have ratified the AMA treaty.

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