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African Vaccine Manufacturing Initiative (AVMI): Briefing Note on the Prioritization of Regulatory Enablers to facilitate accelerated and sustainable African vaccine manufacturing.

The AVMI provides a consensus voice for African Vaccine Manufacturers, specifically within the context of the African Union call for a New Public Health Order aimed at safeguarding the health and economic security of the continent. This encompasses the Africa CDC / Partnership for African Vaccine Manufacturing (PAVM) objective of ensuring at least 60% of Africa's vaccine requirements is supplied by African manufacturers by 2040, up from the unacceptable and dangerously low 1% today.

AVMI considers a progressive regulatory environment at national, regional, continental and at World Health Organisation (WHO) level to be critical to the attainment of Africa's objectives in relation to health security and equity. Furthermore, AVMI believes that developing, producing and supplying vaccines and other countermeasures to internationally recognised standards is vital to ensuring acceptance by all stakeholders of interventions manufactured on the continent.

This briefing note documents AVMI's position and recommendations concerning the Regulatory Environment encompassing its many levels from National to Global (WHO) requirements.

AVMI proposes the following be addressed in order to align the technical and procedural regulatory requirements with the stated strategic intent of the various regulatory stakeholders at each level – namely to support the research & development, manufacture and supply of quality vaccines and other counter measures from African suppliers:

1. National Regulatory Environment – Aligned with the Africa CDC Framework for Action (FFA), continue to build best-in-class National Regulatory Agencies (NRAs) ensuring at least one Maturity Level 3 for vaccine manufacturing (ML3) agency in each region by end 2025.

2. Regional/Continental Regulatory Environment – Aligned with the FFA, and the Partnerships for African Vaccine Manufacturing (PAVM), continuously build the capacities and capabilities of the Regional Centres of Regulatory Excellence (RCOREs) to support mutual recognition, harmonisation and to minimise duplication across the regulatory value chain from pre-submission engagement through to pharmacovigilance reporting. Expedited operationalisation of the African Medicines Agency (AMA) working with the Africa Medicines Regulatory Harmonization Program (AMRH) to develop the African Union (AU) ratified evaluation, release and monitoring processes for the continent. Inclusion of industry representation via the AVMI in the advisory structures of the AMA & AMRH.

3. Global (WHO) Regulatory Environment – Aligned with the WHO's commitment to enhancing global health security and equity in the aftermath of the COVID-19 pandemic, enhance the existing WHO Pre-Qualification (WHO PQ) procedure to accelerate the inclusion of quality interventions available from African suppliers.

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1. National Regulatory Environment

The development of best-in-class NRAs is a critical requirement for the development of a sustainable vaccine manufacturing industry in Africa. NRAs need to be strengthened to enable African manufacturers to achieve WHO PQ, a prerequisite for a vaccine manufacturer to export its products to almost all self-financing countries and those supported by GAVI. To obtain WHO PQ for vaccine products, manufacturers need their NRAs to achieve WHO ML3 status specifically for vaccines.

AVMI congratulates those agencies that have achieved ML3 and welcomes the progress of those working towards its attainment for vaccine manufacturing.

Recommendation:

- The call is for the prioritisation of dedicated resources (human and financial capital) and technical support both within country and from international stakeholders and regional institutions to ensure that at least one NRA per region has attained ML3 for vaccine manufacturing by end 2025
- In addition, and as evidence of Africa's commitment to international quality standards, NRAs aspiring for ML4 for WHO Listed Authority (WLA) status should be fully supported as this will assist in the acceleration of the WHO PQ process (see below).

2. Regional/Continental Regulatory Environment

The PAVM is working through the AMA and AMRH to strengthen the regulatory system for vaccines and develop a harmonized African ecosystem in five keyways:

- By creating a suitable legal environment for NRAs to review vaccine regulatory frameworks and advocate for the implementation of best practices for vaccine manufacturing.
- By harmonizing NRAs' operating models in vaccine manufacturing through greater cross- border collaboration and support to implement continental harmonization initiatives (such as vaccine pre-market authorization).
- By developing vaccine manufacturing knowledge- and expertise-sharing mechanisms between NRAs through multiple South-South partnerships.
- By improving regulation capabilities through upskilling leadership, creating sustainable financing mechanisms, and launching capability-building programs via the development of RCOREs dedicated to vaccine manufacturing regulatory activities.
- By facilitating early NRA engagement to accelerate the rollout of technology transfers.

Recommendation:

- AVMI is supportive of these endeavours and calls for the expedited operationalisation of the AMA to facilitate, working with AMRH, the development of the AU ratified evaluation, release and monitoring processes pertaining to vaccine R&D, manufacturing, registration, and supply for the continent.
- We request industry representation via the AVMI in the advisory structures of the AMA & AMRH.
- AVMI recommends that mutual recognition and reliance mechanisms amongst African ML3 (and above) NRAs be prioritised.

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3. Global (WHO) Regulatory Environment

WHO PQ is a service provided to UNICEF and other United Nations and national agencies that procure vaccines aimed at ensuring that vaccines used in immunization programmes are safe and effective. In prequalifying vaccines, WHO applies international standards and 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 vaccination. WHO PQ also supports the creation and maintenance of a healthy market for vaccines achieved in partnership with GAVI, the Global Alliance for Vaccines and UNICEF.

Before being eligible for WHO PQ, a vaccine must be on the WHO's priority list. The priority categorization of vaccines is established by the WHO in consultation with UNICEF and the Revolving Fund of the Pan American Health Organization (PAHO). Four criteria are used to determine the priority category for each vaccine:

- Demand in UN-supplied markets, including planned new vaccine introductions.
- Suitability for WHO programmatic needs, in compliance with International Health Regulations, eradication, elimination or control initiatives and considerations of individual immunization programmes.
- Recommendations of WHO's Strategic Advisory Group of Experts on immunization.
- Supply security, indicated by the number, diversity and production capacity of suppliers.

The Africa CDC has prioritised 22 diseases classified as being of Legacy, Expanding or Outbreak concern. Five of these do not currently have vaccines available, including the Coalition of Epidemic Preparedness Innovations 'Disease X'. The continental strategy for Africa calls for the production of vaccines addressing these diseases across a range of technology platforms and along all steps of the manufacturing chain.

The WHO target timelines for full PQ assessment are:

- 270 WHO calendar days, if the alternative performance evaluation pathway is selected by the manufacturer
- 350 WHO calendar days, if WHO coordinates the performance evaluation.

Adding in company response and data generation times PQ registration timelines, especially for first- time applicants, can be expected to approach 2 years for this standard process.

The WHO PQ process does however include special considerations for fast-track licensed vaccines (marketing authorization available) that are part of routine immunization programmes, and those that are used only in an emergency response; it is not applicable in the case of novel vaccines not yet introduced or recently introduced into routine immunization programmes.
In agreement with United Nations purchasing agencies or other partners, the fast-track procedure can be considered in the following situations:

- *an acute shortage of a vaccine that puts at risk the global supply of routine immunization programmes and/or an eradication effort;*
- *an emergency situation (i.e. an outbreak or epidemic of a disease for which no prequalified vaccine is available, or where availability is insufficient and an additional source of the same vaccine is required);*
- *exceptional situations such as: – declaration of a pandemic of a disease for which production capacity needs to be established; – need for alternatives to existing vaccines to be used*

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during an eradication effort. Any of the above exceptional situations may lead to acceptance of vaccines for evaluation in parallel to submission to the NRA for marketing authorization purposes upon:

- *special request from the manufacturer; and*
- *endorsement by senior management of WHO.*

In cases where the fast-track procedure is followed, the established deadlines for submission of PSFs do not apply. In addition, the site audit will take place in parallel with quality control tests of samples while the results of tests are pending. There should be maximum flexibility in this process. For example, review of the dossier and testing of samples will be concomitantly performed and the site audit will be conducted as soon as the dossier review is completed.

In recent presentations, for example at the September 2023 UNICEF Vaccine Industry Consultation Meeting, the backlog created by prioritising COVID-19 interventions for PQ emergency review, and the subsequent conversions of these emergency authorisations to routine status was underscored. So too was the finite capacity of the existing WHO PQ team to address the backlog.
AVMI recognises the importance of WHO PQ as an established and internationally recognised standard of medical intervention review and authorisation. In order to align with the stated aim of the WHO to enhance the regionalisation of vaccine and other counter measure manufacturing in Africa, as well as support the effective implementation of other instruments, such as GAVI's African Vaccine Manufacturing Accelerator (AVMA), amendment to the WHO PQ process is required.

Recommendations:

• Africa CDC join UNICEF and PAHO to establish the priority list of vaccines to ensure the needs of the continent are also met.

• The WHO PQ fast track procedure be amended to expressly and progressively facilitate African manufacturers having access to this mechanism in support of regionalisation for enhanced security and equity. This will afford in synchronicity and alignment with both the criteria and timeline of GAVI's AVMA.

• The WHO PQ team liaise with the Africa CDC to explore the recruitment of dedicated staff to handle submissions from African manufacturers.

• African NRAs pursuing ML4 and inclusion in the WLA be progressively supported by the WHO to additionally facilitate acceleration of the WHO PQ process for African manufacturers

Conclusion

AVMI recognises the fundamental importance of a robust and timely regulatory environment at all levels in order for African vaccine manufacturing to develop to maturity and gain acceptance especially with recipients and their careers. The above recommendations are designed to address what AVMI sees as the priority areas requiring redress at the national, regional/continental, and global level in order to more effectively support the AU's call for 60% of the continents vaccines to be made locally by 2040 – a necessity if global health security and equity are to be enhanced in the wake of the global pandemic.

About AVMI: The African Vaccine Manufacturing Initiative is a not-for-profit organisation established in 2012 with the mission of advancing sustainable human vaccine manufacturing capacity in Africa. AVMI is positioned as the voice of African vaccine manufacturing industry representing more than 20 manufacturers on the continent and works closely with the Africa CDC and other key stakeholders in support of the Partnership for African Vaccine Manufacturing (PAVM).