AfriDx Policy Brief

regulating local manufacturing of IVDs in Ghana

EDCTP

AfriDx Diagnostic Project

Executive Summary

Local manufacturing of diagnostics has the potential to create revenues, jobs and high value exports and reduce health spending. It promotes capacity and know-how held by local researchers and entrepreneurs who can apply or adapt it to other problems (i.e. transferability), ensuring that products are designed for the needs of the local healthcare systems, and creating greater autonomy and resilience. Strengthening local research, innovation and industry while lowering healthcare costs lays a path for the lasting, systemic change required for low and middle income countries (LMICs) to deal with COVID-19, future pandemics and their day-to-day healthcare needs.

To enable all of these potential benefits, stringent regulation of locally manufactured diagnostics is essential to ensure that they are safe and effective. However, many LMIC regulatory bodies do not have mature pathways, legal texts and experience for regulating locally manufacturing of *in vitro* diagnostics (IVDs).

AfriDx is a UK-Denmark-Ghana initiative to develop systems for the clinical diagnosis of Covid-19 designed to be manufactured in low and middle-income countries. We considered it essential to better understand the regulatory landscape in Ghana and any recommendation that could be made which would ease the path of local manufacturers to bring products to market. In this policy brief we describe the process for gaining regulatory approval of locally manufactured IVDs in Ghana. Ghana is generally considered to have a mature regulatory capacity and unlike many countries in Sub-Saharan Africa, it has a route for regulating locally manufactured IVDs.

We then propose the following key policy recommendations to facilitate future regulation of locally manufactured IVDs in Ghana:

1. Efforts for regulatory alignment across the ECOWAS region should be accelerated. This could greatly enable local manufacturers to expand their markets to neighbouring countries without duplication of effort. Expansion is likely to be essential to collate sufficient market demand

2. Regulatory bodies like the Ghana FDA should continue to provide support to local innovators and manufacturers through willingness to communicate, clear documentation and feedback mechanisms.

3. Navigating the fragmented regulatory landscape and entering processes like WHO prequalification will often require external support from experienced IVD regulatory experts. As these skills are not common in Ghana, one action for an intergovernmental organisation or an international NGO would be to facilitate local manufacturers to find and access appropriate regulatory support.

Local Manufacturing of IVDs

The COVID-19 pandemic has highlighted the need to strengthen the research, development, manufacturing, supply and accessibility of diagnostics to low- and middle- income countries (LMICs). Although the pandemic resulted in increased funding for diagnostic research and development, this has been overwhelmingly focused in high income countries (HICs). Access to diagnostics in LMICs has also received attention, including through the World Health Organisation's Access to Covid-19 Tools Accelerator (WHO ACT-A) but the focus of most initiatives to date has largely been procurement, R&D and market readiness rather than bolstering manufacturing capacity in LMICs.

However, numerous African government reports since 2000[1,2] have highlighted the potential for developmental synergies to be extracted between expansion of industrial production of medical supplies and improvement of the coverage and quality of health care, especially for their low-income populations. In May 2019[3], six international organisations with influence on global health (WHO, UNIDO, UNCTAD, UNAIDS, UNICEF and The Global Fund) released a joint statement promoting local production of medicines and health technologies, laying out the need for "effective multisectoral collaboration in order to promote enabling investment, legal and technical environments".

Local manufacturing has the potential to create revenues, jobs and high value exports and reduce health spending. It promotes capacity and know-how held by local researchers and entrepreneurs who can apply or adapt it to other problems (i.e. transferability), ensuring that products are designed for the needs of the local healthcare systems, and creating greater autonomy and resilience. Strengthening local research, innovation and industry while lowering healthcare costs lays a path for the lasting, systemic change required for low and middle income countries (LMICs) to deal with COVID-19, future pandemics and their day-to-day healthcare needs.

Regulation of locally manufactured diagnostics is essential to ensure that they are safe and effective. However, many LMIC regulatory bodies do not have mature pathways, legal texts and experience for regulating locally manufacturing of IVDs. The IVD sub-sector is regulated inconsistently relative to other areas of the health industry and regulation is often tied to the service delivery model e.g. lab-administered testing, clinical point-of-care test, home testing. COVID has highlighted the needs for regulatory pathway strengthening not only for locally manufactured IVDs but also for imports.

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[1] Mackintosh, M; Banda, G; Tunguhole, J; (2017) Local production of pharmaceuticals and health system strengthening in Africa. [Review]. German Health Practice Collection. https://discovery.ucl.ac.uk/id/eprint/10044381/

[2] Srinivas in Mackintosh et al (Eds) Making medicines in Africa ISBN 978-1-137-54647-0. https://link.springer.com/book/10.1007/978-1-137-54647-0

[3] WHO (2019). Interagency Statement on Promoting Local Production of Medicines and other Health Technologieshttps://www.who.int/publications/m/item/interagency-statement-on-promoting-local-production-of-medicines-and-other-health-technologies

policy brief we describe the process for gaining regulatory approval of locally manufactured IVDs in Ghana and highlight key policy recommendations to facilitate future regulation.

Introduction to IVD Regulation in Ghana

In Vitro Diagnostic Medical Devices (IVDs) are defined by the Ghana FDA as:

"A device, whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes. This includes reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles."

IVDs are regulated under the same Ghanaian law as Medical Devices (MDs): Section 148 of the Public Health Act, 2012, Act 851. It is a requirement for all devices that are "manufactured, prepared, imported, exported, distributed, sold, supplied, or exhibited for sale" to be registered with the FDA by their manufacturers, importers and distributors. Anyone conducting clinical trials of IVDs must also register with the FDA and be issued a certificate before proceeding.

Responsibility for developing regulatory requirements and for evaluation and registration of all classes of medical devices falls to the Medical Devices Department (MDD) within the FDA. As with most MD regulatory frameworks, the intention of the MDD is to ensure that medical devices are safe, effective, and manufactured from premises that meet the codes of current good manufacturing practices (cGMPs).

At a minimum the manufacturer is required to demonstrate:

- a functional quality management system (QMS)
- a system for post-market surveillance
- technical documentation
- declaration of conformity
- registration of the manufacturing facility and the medical devices.

They have the broader obligation of ensuring that the IVD meets relevant safety and effectiveness requirements. These requirements may differ per IVD and may be defined by the regulator (particularly for diseases of public health concern) or by other bodies like the WHO. IVDs for newer diseases or those of limited public health concern may need to be justified by the manufacturer and assessed ad hoc by the FDA. In addition to stating how the IVD specifications meet safety and effectiveness requirements, the manufacturer also needs to keep objective evidence that the IVD meets those requirements.

The full information is provided via FDA Document DA/MDD/FOR-04 "Application Form for the Registration of Class II-IV Medical Devices". Samples of the device will normally be required for testing. All of the above information would need to be submitted by a local manufacturer or for foreign manufactured products, by a local representative such as an agent or distributor who is resident in Ghana. We have outlined the process to gain a Medical Device manufacturing licence and an IVD product registration in Fig 1.

Ghana is generally considered to have a mature regulatory capacity and unlike many countries in Sub-Saharan Africa, it has a route for regulating locally manufactured IVDs. This is evidenced by

the available options on FDA IVD registration forms and by the successful registration of locally manufactured diagnostics in the past, per reports from KNUST partners and Incas Diagnostics who have rapid tests for pregnancy and sexually transmitted diseases on the market.

We gathered data on their experience working with the Ghana FDA to regulate locally manufactured IVDs. They reported that the FDA is straightforward to contact and very willing to sit down for a conversation, having particular interest in supporting local IVD innovation and manufacturing. They also confirmed that the process and forms described on the Ghana FDA website are accurate and that their experience of completing them and submitting for review was smooth. The willingness of the FDA to engage with local manufacturers is advantageous to any efforts made by initiative such as AfriDx to manufacture and regulate IVD reagents, assays or entire devices.

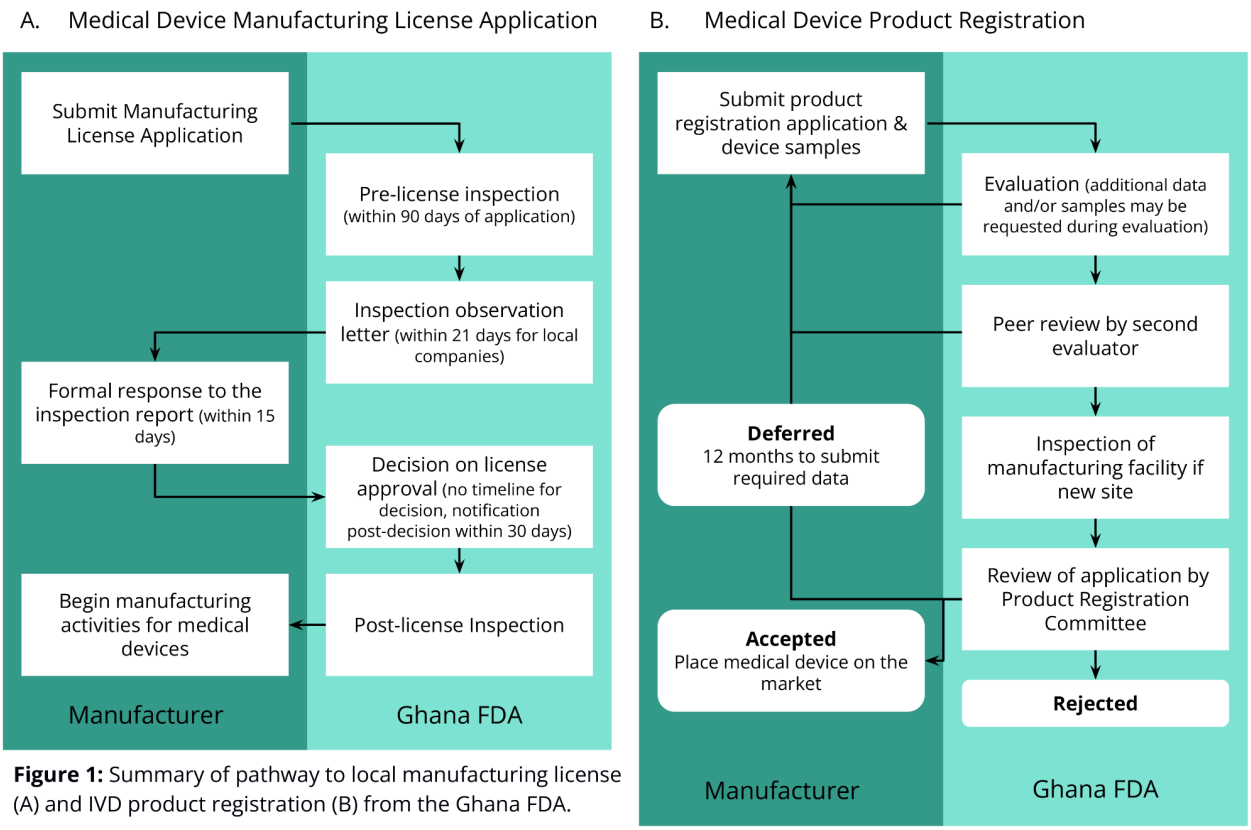

Figure 1: Summary of pathway to local manufacturing license (A) and IVD product registration (B) from the Ghana FDA.

Timeline for regulatory approval

The FDA states that all new applications and applications for renewal would be processed within a minimum period of six months but an application may be expedited if the product is for public health programmes e.g. HIV/AIDS, malaria, tuberculosis, reproductive health, Neglected Tropical Diseases (NTDs) or other disease conditions as determined by the FDA.

For a new manufacturer, the requirement for an inspection of the manufacturing site is likely to delay the procedure compared to an existing manufacturer. Trying to register a Class IV IVD will also result in the most stringent assessment procedures. There is no publicly accessible data in terms of time to approval for the Ghana FDA but in correspondence with KNUST partners and the Ghanaian diagnostics company Incas Global, an estimate of 18-24 months to complete the whole

process seems realistic. For a pre-registered manufacturer, the process could be 12 months and potentially faster if the IVD has been regulated by another stringent NRA and can go through the Reliance Pathway (Section 3.5).

This refers to a situation where the Ghana FDA will rely on approvals by a well-resourced or reference National Regulatory Authority which speeds up the process of registration in Ghana. In this case the manufacturer submits the full assessment report from the other NRA, a full Clinical Trial Application or a full product development dossier and await a decision whether the product is authorised to go through the reliance pathway. If accepted the Ghana FDA could rely partly or fully on third party dossier assessment reports, GMP/GCP inspection reports and QC laboratory reports.

Ghana in the Context of IVD Regulation in Africa

In comparative studies, Ghana's regulatory process for registration of imported products is described as being less complex and more efficient than many other countries. For example, Puigvert & Zollini[4] (2020) researched regulation of HIV self tests in 26 African countries and found that those with the least complex regulatory process are Ghana, Sierra Leone, Ethiopia, Nigeria and Rwanda. These also tended to be places where written communication was efficient whereas the presence of a local partner or proxy simplified communications in Lesotho and Swaziland. Some countries relied on extraordinary meetings with external advisors (Botswana and Guinea-Bissau), had unforeseen and ad hoc requests due to lack of clarity of process (DR Congo and Burkina Faso) or lacked capacity to proceed with regulating a HIV self-test as the regulatory process was still being established (Côte d'Ivoire).

An important factor is also the type of testing being proposed and the intersection of IVD regulation and health policy may be complex. For example, Puigvert & Zollini (2020) reported that HIV self-tests are banned in some countries (e.g. Tanzania) or countries were still discussing acceptance criteria and policies, creating an indefinite delay in product registration.

This study also revealed that in the African territories there is a high involvement of external advisors in the approval for the HIV-ST kits, particularly predominant is the role of the WHO prequalification and recommendations. Among the latters, it is remarkable the implementation of pilot programs, including field research to determine which distribution models would yield the best outcomes. This process has a strong influence in the planning of the HIVST kits approval and distribution as these activities may take years to be completed, and some countries are not willing to grant regulatory approval for the product before the pilot programs are complete.

The other countries we are aware of which have active domestic IVD manufacturing are Senegal, Kenya, Ethiopia and South Africa. These countries therefore have a proven record in terms of the regulatory pathway. For COVID testing, South Africa did not approve any locally developed tests for 18 months despite having a mature regulatory authority (SAPHRA). All local manufacturers surveyed as part of the AfriDx key opinion leader survey reported that there were limitations in the regulatory pathway. In particular, being able to register reagents and raw materials with local

[4] Puigvert, Ana Lucia, and Maria Zollini. "Challenges to obtain the Regulatory approval for an HIV Self-Test kit in African Countries-case study: Technical Article." Revista Argentina de Bioingeniería 24.5 (2020): 77-81.

registration authorities, indicating that there is still work necessary both in Ghana and across the continent.

Regulatory Fragmentation

Regulation is complicated by fragmentation: the majority of regulation happens on a country by country basis with limited portability. There is an effort to harmonise medical product regulations in the Economic Community of West African States (ECOWAS) region which includes Gahna. This is known as the West Africa Medicines Regulations Harmonization (WA-MRH) project. It has been primarily focused on medicines but expressions of interest[5] for the ECOWAS Joint Assessment Procedure since 2021 included IVDs for SARS-CoV-2 which may precede the broader inclusion of IVDs and other medical devices. This evaluation would be led by Nigeria and would be substantially more expensive than a national application in Ghana, costing $23,750 in total, subsidised to $8,000 in recent calls for applicants in the West Africa Region.

Another approach would be to register the product with a stringent authority such that the Ghana FDA would regulate via the Reliance Pathway, allowing them to expedite the process. This would also be helpful to bring IVDs to market outside of Ghana. Many countries have similar pathways depending on stringent NRAs in the US or Europe. The most common certification accepted across African countries is WHO prequalification (PQ), making this one of the optimal routes to market across the continent for those products that are eligible for PQ, including SARS-CoV-2 tests. This process enables expedited regulation in many African countries as well as enabling supply via UN programmes.

However, seeking US FDA, European regulatory approval or WHO PQ can add significant up front cost and time investment for an LMIC manufacturer.

Selecting a Regulatory Pathway

Manufacturing a whole IVD in-country would be the most complex regulatory pathway, particularly if the prospective manufacturer does not yet have an existing licence for manufacturing medical devices. This would need to be approved in addition to the product registrations. This process is likely to take at least 18-24 months.

A middle ground would be to use manufacturers in other countries that already have ISO13485 compliant manufacturing and/or register the product with a stringent authority such that the Ghana FDA would regulate via the Reliance Pathway, allowing them to expedite the process. This would also be helpful to bring IVDs to market outside of Ghana. Many countries have similar pathways depending on stringent NRAs in the US or Europe. The most common certification accepted across African countries is WHO prequalification, making this one of the optimal routes to market across the continent for those products that are eligible for PQ, including SARS-CoV-2 tests.

[5] https://fdaghana.gov.gh/img/reports/WAHO%20TENDERS.pdf

Policy Recommendations

Based on our exploration of regulating local manufacturing of IVDs in Ghana, we propose the following key policy recommendations to facilitate future regulation of locally manufactured IVDs in Ghana:

1. Efforts for regulatory alignment across the ECOWAS region should be accelerated. This could greatly enable local manufacturers to expand their markets to neighbouring countries without duplication of effort. Expansion is likely to be essential to collate sufficient market demand

2. Regulatory bodies like the Ghana FDA should continue to provide support to local innovators and manufacturers through willingness to communicate, clear documentation and feedback mechanisms.

3. Navigating the fragmented regulatory landscape and entering processes like WHO prequalification will often require external support from experienced IVD regulatory experts. As these skills are not common in Ghana, one action for an intergovernmental organisation or an international NGO would be to facilitate local manufacturers to find and access appropriate regulatory support.

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