SUPPLEMENT ARTICLE

Regulatory In Vitro Diagnostics Landscape in Africa: Update on Regional Activities

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Improved diagnostic tests for tuberculosis case detection are urgently needed that are affordable, robust, and easy to use so that they can be implemented widely. The mandate of national regulatory authorities is to ensure the safety and effectiveness of diagnostics, protecting the population against unsafe products while expediting access to beneficial new devices. However, regulatory approval processes in the developing world are often complex, lengthy, and not transparent. Recent progress in building regulatory capacity using harmonized approaches will reduce duplication in clinical performance studies and manufacturing audits, facilitate information sharing through trust and mutual confidence building, and ultimately improve efficiency. These savings can be passed onto the consumers in the form of more affordable pricing and allowing new high-quality tests for tuberculosis to be introduced more quickly and without delay.

Keywords. regulation; diagnostic tests; harmonization; tuberculosis.

Considerable progress has been made in controlling tuberculosis with improved treatment success rates and declining mortality, but efforts to contain the disease are hampered by low rates of detection, particularly in regions such as sub-Saharan Africa where only half of the estimated incident cases are notified [1]. The need for improved diagnostic tools has been recognized by the STOP TB movement, but the perceived lack of a financial return has discouraged commercial investment in new tests that can be widely implemented in resource-limited settings [2]. In recent years, simple rapid serology tests to detect antibodies to *Mycobacterium tuberculosis* have been marketed, but evaluation of these tests showed that they are neither sensitive nor specific for tuberculosis case detection [3, 4]. However, the absence of regulatory controls in most developing countries has allowed these products to enter the market. In addition to concerns for public safety, unregulated tests of poor quality make it difficult for companies with high-quality products, which are often more expensive, to compete in markets flooded with such tests. This article reviews the regulation of diagnostic tests for tuberculosis case detection with a focus on the World Health Organization (WHO) region of Africa, an area of high tuberculosis morbidity and mortality and where the disease remains a public health emergency.

REGULATION OF MEDICAL DEVICES, INCLUDING IN VITRO DIAGNOSTICS

Medical devices can be grouped broadly into 3 categories: (1) active implantables (eg, cardiac pacemakers); (2) general medical devices (eg, scalpels and scanners); and (3) in vitro diagnostics (IVDs). The major distinction between the 3 categories is that IVDs use specimens taken from the body whereas the other medical devices are used either in contact with or implanted into the body. IVDs range from sophisticated instruments to simple lateral flow devices suitable for home use.

The primary goal of regulation is to protect public health and safety. Guiding principles issued by the Pan American Health Organization, the Regional Office for the Americas of the WHO, and the US Food and Drug Administration (FDA) in 1991 state that regulatory

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1. The primary goal is to protect public health and safety.
2. A regulatory system should ensure that valuable new technologies are made available to the clinical community and to patients and consumers expeditiously while preventing unsafe or ineffective devices from reaching the market.
3. Regulatory decisions must be based on strong and clear science, free of external influences and consistent with the directives of law.
4. As the guarantor of public health, enforcement of the law must be vigorously, fairly and uniformly carried out and appropriate regulatory and legal actions taken against violators.
5. Government-prescribed rules and procedures must be clearly articulated for those who must comply with them.
6. Assuring medical device safety requires oversight of the use of medical devices.
7. Information on product risks must be openly communicated with health professionals and consumers.
8. Countries instituting medical device programs should be cognizant of ongoing international harmonization efforts.

Figure 1. Guiding principles for regulation of medical devices [5].

decisions should be based on strong and clear science and be free of external influences (Figure 1) [5]. In the developing world, regulatory pathways are varied, often costly, lengthy, and not transparent. While ensuring the quality and safety of diagnostic tests is an important aspiration, the cost to a manufacturer of complying with complex regulatory approval processes is often considerable and can result in increased pricing, making products less affordable [6]. Delay in gaining access to the market due to protracted premarket approval processes may also deprive patients of access to new diagnostic tests [7]. This is particularly important in developing countries where laboratory services may not be available or affordable, and where the benefits of simple rapid tests that can increase access to diagnosis could be substantial.

Because there are thousands of IVDs, it is beyond the capacity of any national regulatory authority (NRA) to regulate all of them. The guiding principles published by WHO and the FDA recommend that the degree of regulation be proportionate to the potential harm from a product, as no test is perfect [5]. Regulators need to decide whether the potential benefits of using a medical device or IVD outweigh the potential risks to both the individual and to the public, where risk is a combination of the severity of harm and the probability of its occurrence (Table 1) [8]. With the notable exceptions of the United States and Japan, most NRAs and the WHO have adopted a 4-tier risk classification system (Table 2). Tests to ensure safety of blood products, where a false-negative test result would put recipients at risk of contracting a life-threatening disease, are considered high-risk products, whereas tests for noncritical conditions and general laboratory reagents pose less risk and thus require lower levels of scrutiny.

NRAs work within a legislative framework that allows the enforcement of regulatory requirements of the country. Prior to market approval, new tests are assessed by consideration of their precision, clinical performance (sensitivity, specificity, and reproducibility), and quality of manufacture. Regulatory reviews do not take into account clinical impact or cost effectiveness. Studies to investigate the impact of a new test on patient outcomes such as morbidity or mortality are programmatic decisions that are normally undertaken subsequent to regulatory approval.

Table 1. Risk Classification Categories for In Vitro Diagnostics Regulation

Classification	Personal Health Risk	Public Health Risk	Examples
Class A	Low	Low	Stains, culture media
Class B	Moderate	Low	Home use pregnancy tests
Class C	High	Moderate	Tests for tuberculosis
Class D	High	High	Blood screening tests, eg, HIV

Adapted from Global Harmonization Task Force recommendations [8].
Abbreviation: HIV, human immunodeficiency virus.

Table 2. Examples of In Vitro Diagnostics Classification Among the Global Harmonization Task Force Founding Members

United States	European Union	Australia	Canada	Japan
Class I Microbiologic culture media, general-purpose reagents	List A HIV, HBV, HCV, HDV, HTLV, ABO blood typing	Class I Laboratory equipment, reagents, specimen receptacles, and microbiologic culture media	Class I Microbiological culture media	Class I Liver function tests, LDH, estradiol
Class II Syphilis, PSA	List B PSA, rubella, blood sugar self-test	Class II Sodium, ALT, LDH, ferritin, or folate	Class II Ferritin test	Class II Blood cell morphology, autoimmune markers
	Others: List non-A/non-B: TB	Class III Syphilis (RPR), typhoid, Q Fever, *Chlamydia trachomatis*	Class III Self-test of blood glucose	
Class III HIV, HBV, HCV, HTLV, ABO blood typing TB		Class IV HIV, HCV, HBV, HTLV test; and any confirmatory assays used to screen blood and tissue in selected populations, including CMV, dengue, malaria, TB	Class IV HIV, HBV, HCV, HTLV, ABO blood typing, TB	Class III HIV, HCV, tumor markers, microbiology including TB

Abbreviations: ALT, alanine aminotransferase; CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; HTLV, human T-lymphotropic virus; LDH, lactate dehydrogenase; PSA, prostate-specific antigen; RPR, rapid plasma reagin; TB, tuberculosis.

REGULATION OF TUBERCULOSIS TESTS

The main hazards associated with IVDs stem from incorrect or misleading test results. For tuberculosis, a missed diagnosis not only denies a patient access to effective therapy, but also poses a public health risk of allowing the ongoing transmission of the disease. Conversely, a false-positive result may result in unnecessary chemotherapy with antituberculosis medication. For these reasons, most NRAs classify tuberculosis tests as risk class III or C. Manufacturers seeking approval to market a new tuberculosis diagnostic test that has been designated class III or C would be required to submit a dossier compiling a full description of the product, the manufacturing process, a statement of intended use, copies of package inserts and user instructions, and evidence of analytical accuracy and clinical performance. Clinical performance studies should be undertaken in the target populations at sites of intended use and where the test was performed by the intended users. Such studies and subsequent analysis of the results should be free from interference from the test developers or their agents. The NRA will also examine the quality management system of the manufacturer, including reports from a site visit by a team of experts.

When assessing a device for premarket approval, NRAs will also take into account local demographic, epidemiologic, and environmental factors that may alter the performance of a test. Examples of factors that influence tuberculosis tests are immunosuppression caused by coinfection with human immunodeficiency virus (HIV) [9, 10], instability of electrical supplies, and temperature and dust levels at the testing sites [11–13]. NRAs also consider the local health infrastructure and availability of supportive services that might influence the severity of harm. Thus, a test for multidrug-resistant tuberculosis that gives false-positive results risks unnecessary patient exposure to toxic second-line tuberculosis drugs, but such a test might be acceptable in settings where confirmatory tests are available. Following premarket approval, regulators continue to protect the public through advertising controls that prevent misleading claims about test performance and ensure clarity of intended use. Postmarket vigilance ensures that satisfactory quality is maintained throughout the life of a product, either by active surveillance measures, such as batch testing to check quality, or by monitoring complaints.

In contrast, a low-risk test such as culture media or a new staining kit for acid-fast bacteria would face less scrutiny. The manufacturers would be required to submit a dossier describing the product, including technical specifications such as shelf life, but clinical performance studies would not normally be requested. Similarly, such a product would not require active postmarketing surveillance from the NRA.

A recent example of premarket regulatory approval for a new tuberculosis test is the FDA's approval for Xpert MTB/RIF (Cepheid) [14]. Following technical review of the quality and safety of the device and examination of the evidence of analytical accuracy and clinical performance, the test was approved for use on raw sputum or concentrated sediments prepared from induced or expectorated sputum from patients for whom there is clinical suspicion of tuberculosis and who have received no antituberculosis therapy or <3 days of therapy. The FDA recommended that the intended use statement of this test include that the test is intended as an aid in the diagnosis of pulmonary tuberculosis when used in conjunction with clinical and other laboratory findings; following a risk-benefit analysis, approval was

granted with the recommendation that culture also be performed. Regulators in tuberculosis-endemic countries would need to consider the risks to their population of the test operating in a more challenging environment and where confirmatory testing might not be available.

THE GLOBAL REGULATORY LANDSCAPE

Regulation of IVDs ranges from highly stringent environments found in high-income countries to no effective control, as is the case in most low-income countries [15–17]. Requirements for premarket approval vary across NRAs and, with the exception of countries of the European Union, manufacturers must prepare product dossiers tailored to individual countries and in different languages, a time-consuming and costly undertaking. Inefficient premarket approval processes with avoidable delays and unnecessary duplication are not uncommon, making regulation a significant impediment to market entry and a disincentive to innovation. Conversely, implementation of new technology without due consideration of local circumstances may result in inappropriate use of tests, with heightened risks to public health.

In recognition of the need for standardized regulation, international fora have been established with the goal of promoting international trade and increasing access to new technology through a more harmonized approach. The Global Harmonization Task Force (GHTF), a voluntary body of regulators and industry representatives from Australia, Canada, the European Union, Japan, and the United States, worked from 1992 to 2012 to produce a series of consensus documents on the principles and guidance for a harmonized regulatory system for medical devices. These principles have been further elaborated by the Asian Harmonization Working Party (AHWP), which is a voluntary body of 24 member economies and industry. The AHWP has produced a series of more practical guidelines for regulating medical devices. The GHTF was disbanded in 2012 and in its place is the International Medical Devices Regulatory Forum (IMDRF), a voluntary group of regulators from Australia, Brazil, Canada, China, the European Union, Japan, the Russian Federation, and the United States. The aim of the IMDRF is to accelerate international medical device regulatory harmonization and convergence. Regulators from Africa, Asia, and Latin America and medical device manufacturer associations can attend their meetings, and 2 nonregulatory bodies (WHO and the Life Sciences Innovation Forum of the Asia-Pacific Economic Community) have observer status.

THE AFRICAN REGULATORY LANDSCAPE

Although most African countries have national bodies that oversee the registration of medicines, few have capacity to regulate IVDs, and manufacturers are faced with a plethora of requirements when they seek to register a new test. In the absence of formal transparent mechanisms for regulatory control, some national disease control programs or Ministries of Health oblige companies to undertake product evaluation studies in a local laboratory, which can result in unnecessary and costly duplication. The company that marketed the first point-of-care test for CD4 cell count has to conduct >60 evaluation studies as part of its global rollout [6], a requirement that has delayed access for some populations to a test that would determine their eligibility for life-saving antiretroviral therapy.

A survey of East African Community (EAC) Partner States in 2012 found that regulation of IVDs was a neglected area [16]. Although the majority of States had a legal framework for regulating medical products, their capacity to regulate IVDs was limited (Table 3). A few laboratories were reported to have assessed the performance of new tests for diseases such as tuberculosis, HIV, and malaria, but postmarketing surveillance was rare. In some countries, processes for registering IVDs were ambiguous, and tensions were evident between organizations whose primary function was to oversee the clinical laboratories and technical personnel and regulatory agencies whose primary activity was the regulation of medicines. Activities to strengthen diagnostics regulation in the region are being pursued, and agreement has been reached to harmonize regulation of IVDs across the EAC. In-country efforts include the creation of a national Food and Drug Authority in Rwanda, with a mandate to regulate all medical products. In Tanzania, the FDA has now built capacity to regulate medical devices with support from WHO, and a pilot project on postmarketing surveillance has been undertaken. In the absence of a regulatory authority, South Africa has relied on advice from the National Health Laboratory Service, but in 2014 a decision was taken to augment the role of the Medicines Control Council to include regulation of IVDs in preparation for the creation of the South African Health Products Regulatory Authority, which will be a statutory regulatory authority.

Some countries in Africa are dependent on donor support for the procurement of IVDs and other health products. The tests they receive may be subject to scrutiny by the donating agency. In the absence of stringent control of products for the African market, some US-based organizations seek advice from the US Centers for Disease Control and Prevention. Although not a regulatory body, WHO has set up a prequalification program to carry out scrutiny on some priority medical products, including IVDs for malaria and HIV (but not tuberculosis tests). African NRAs may take WHO prequalification, or approval by well-established NRAs such as the FDA and European Union (CE marking), into consideration when reviewing applications, thereby accelerating the process of premarket approval. The WHO has adopted a process of endorsing technologies for detecting tuberculosis for policy recommendations based on evidence from the

Table 3. Regulation of In Vitro Diagnostics in Africa

Regulations	Burundi	Kenya	Rwanda	Tanzania	Tanzania/ Zanzibar	Uganda	Ethiopia	Nigeria	South Africa
Legal framework	✓	✓	✓	✓	✓	–	✓	✓	✓
IVD regulated?	–	✓	–	✓	✓	–	✓	✓	✓
Premarket controls									
Adoption of GHTF classification	–	–	–	✓	✓	–	✓	In process	✓
Registration	–	+	–	✓	–	–	✓	✓	✓
Clinical performance Evaluation capacity	+	✓	–	✓ Limited	–	✓ HIV only	✓ Limited	–	✓
Manufacturing audit	–	–	–	–	–	–	–	–	–
Marketing controls									
Advertising control	✓	+	–	✓	–	✓	✓	✓	✓
Marketing controls	–	+	HIV, TB	✓	–	✓	✓	✓	✓
Postmarketing controls									
Surveillance	–	+	–	✓	–	–	–	–	✓
Accredited laboratories	–	✓	–	✓	–	✓	✓	–	✓
Device reporting	–	+	–	–	–	–	–	–	✓
Corrections/recall	–	+	–	–	–	–	–	–	✓

Abbreviations: GHTF, Global Harmonization Task Force; HIV, human immunodeficiency virus; IVD, in vitro diagnostics; TB, tuberculosis.

scientific literature, including studies undertaken by the test developers. Indiscriminate adoption of new technologies can lead to inappropriate placement [18], and assessment by an NRA with clear recommendations on their use is highly desirable.

REGULATORY HARMONIZATION IN AFRICA

Harmonization reduces registration timelines for applications, facilitates information sharing through trust and mutual confidence building, and ultimately saves time and money. These savings can be passed onto the consumers in the form of more affordable pricing.

The Pan African Harmonisation Working Party on medical devices and diagnostics (PAHWP) is a voluntary body that aims to improve access to safe and affordable medical devices and diagnostics in Africa through harmonized regulation. The PAHWP was conceived in 2012 following stakeholder meetings in East Africa and launched in December 2012. Founding members include the EAC Health Secretariat and the EAC Partner States (the Republic of Kenya, the Republic of Uganda, the Republic of Burundi, the Republic of Rwanda, and the United Republic of Tanzania), Ethiopia, Nigeria, South Africa, and the London School of Hygiene and Tropical Medicine. Partners include German International Co-operation, the African Society for Laboratory Medicine, and WHO (Regional Office for Africa and Headquarters). Meetings have also been held with counterpart organizations in Asia and Latin America. PAHWP is anchored within the AU-NEPAD agency regulatory harmonization program alongside the African Medicines Regulatory Harmonization initiative. PAHWP studies and recommends ways to harmonize medical devices and diagnostics regulation in Africa, and the current priority is in vitro diagnostic devices. Efforts are under way to engage other regional economic communities, interested member states, and industry associations. Three African fora on the regulation of IVD, held during 2014, were attended by regulators, industry representatives, laboratory experts, and other stakeholders. AHWP has prepared a Playbook for Regulation of Medical Devices. At the third African Regulatory Forum, the Playbook was introduced and PAHWP recommended that countries adopt a stepwise approach to harmonized regulation. The vision is that transparent regulatory processes with clear guidelines and harmonized requirements for dossier submission, procedures, and standards will lead to a streamlined and faster approval. Priorities include establishing a laboratory network and communications platform for postmarketing surveillance activities and reducing unnecessary duplication in clinical performance studies. Plans also include establishment of a resource and learning center to promote pooling and sharing of resources and capacity building through e-learning from a virtual campus. The decision of the EAC to harmonize regulation across the 5 Partner States with a combined population of 135 million represents a significant step forward in reducing trade barriers in the region and has been warmly welcomed by the diagnostics industry.

Countries in southern Africa are also keen to meet the mandate of providing access to safe, affordable, quality medicines. Where countries have similar evaluation and registration processes, collaboration on medicines registration can accelerate public access to quality-assured medicines. To this end, national medicines regulatory authorities in Zambia, Zimbabwe, Botswana,

and Namibia, with support from the WHO prequalification team, have formed the Zazibona initiative and are undertaking pilot collaborative activities in both medicines and diagnostics. The pilot collaboration, as agreed among involved authorities and WHO in mid-2013, represents an example of synergizing and harmonizing activities as advocated by the third African Medicines Regulatory Authorities Conference, held in Johannesburg in December 2013 [19].

Trans-regional links continue to grow. South Africa and Tanzania are now members of AHWP, and Ghana and Kenya have joined the AHWP Working Group 2 on IVDs. Harmonized approval for IVDs will soon be a reality.

CONCLUSIONS

Regulation of medical products is intended to ensure safety and quality while ensuring timely access to beneficial new products. The current regulatory landscape for diagnostic tests in developing countries acts as a disincentive to innovation and a barrier to new diagnostic products entering those markets. Weak regulation allows poor-quality tests to be marketed, and nontransparent, lengthy regulation causes unnecessary delay and increases costs. There has been considerable progress in regulatory capacity building and harmonization in Africa in the last 2 years. Harmonized approval of diagnostics can soon be a reality, removing barriers to market entry and allowing high-quality tests to be more affordable and introduced without delay.

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