Increasing Access to Diagnostics Through Technology Transfer and Local Production
Increasing Access to Diagnostics Through Technology Transfer and Local Production
Prepared for the WHO Department of Public Health, Innovation and Intellectual Property by Rosanna Peeling and Ruth McNerney (London School of Hygiene & Tropical Medicine).

This report forms part of the project entitled: Improving access to medicines in developing countries through technology transfer related to medical products and local production. It is implemented by the Department of Public Health Innovation and Intellectual Property of the World Health Organization (WHO/PHI) in partnership with the United Nations Conference on Trade and Development (UNCTAD) and the International Centre for Trade and Sustainable Development (ICTSD) with funding from the European Union (EU). The overall objective of the project is to increase access – especially for the poor in developing and least developed countries – to medicines, vaccines and diagnostics.

All reports associated with this project are available for free download from the following website: http://www.who.int/phi/en/

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Editing and design by Inís Communication – www.iniscommunication.com

WHO Library Cataloguing-in-Publication Data

Increasing access to diagnostics through technology transfer and local production.

1. Diagnostic tests, Routine. 2. Technology transfer. 3. Developing countries. I. World Health Organization.


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Printed in France

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<th>Full Form</th>
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<tr>
<td>AHWP</td>
<td>Asia Harmonization Working Party</td>
</tr>
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<td>ANDI</td>
<td>African Network for Drugs and Diagnostics Innovation</td>
</tr>
<tr>
<td>ANVISA</td>
<td>National Health Surveillance Agency</td>
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<tr>
<td>ASEAN</td>
<td>Association of South-East Asian Nations</td>
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<tr>
<td>CAGR</td>
<td>compound annual growth rate</td>
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<tr>
<td>CE</td>
<td>Conformité européenne</td>
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<tr>
<td>DALY</td>
<td>disability-adjusted life-year</td>
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<td>DPP</td>
<td>Dual Path Platform</td>
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<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
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<tr>
<td>EU</td>
<td>European Union</td>
</tr>
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<td>FDA</td>
<td>United States Food and Drug Administration</td>
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<td>FIND</td>
<td>Foundation for Innovative New Diagnostics</td>
</tr>
<tr>
<td>Fiocruz</td>
<td>Oswaldo Cruz Foundation</td>
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<tr>
<td>GDP</td>
<td>gross domestic product</td>
</tr>
<tr>
<td>GHTF</td>
<td>Global Harmonization Task Force</td>
</tr>
<tr>
<td>GLP</td>
<td>good laboratory practice</td>
</tr>
<tr>
<td>GMP</td>
<td>good manufacturing practice</td>
</tr>
<tr>
<td>GSPA-PHI</td>
<td>Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property</td>
</tr>
<tr>
<td>HCG</td>
<td>human chorionic gonadotrophin</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>IFPMA</td>
<td>International Federation of Pharmaceutical Manufacturers and Associations</td>
</tr>
<tr>
<td>IMCI</td>
<td>Integrated Management of Childhood Illness</td>
</tr>
<tr>
<td>ISO</td>
<td>International Organization for Standardization</td>
</tr>
<tr>
<td>IVD</td>
<td>in vitro diagnostic</td>
</tr>
<tr>
<td>JICA</td>
<td>Japanese International Cooperation Agency</td>
</tr>
<tr>
<td>KEMRI</td>
<td>Kenyan Medical Research Institute</td>
</tr>
<tr>
<td>LMIC</td>
<td>low- and middle-income country</td>
</tr>
<tr>
<td>MGIT</td>
<td>mycobacteria growth indicator tube</td>
</tr>
<tr>
<td>NDI</td>
<td>Asian Network for Drugs and Diagnostics Innovation</td>
</tr>
<tr>
<td>NGO</td>
<td>nongovernmental organization</td>
</tr>
<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
</tr>
<tr>
<td>PATH</td>
<td>Program for Appropriate Technology in Health</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>PEPFAR</td>
<td>United States President’s Emergency Plan for AIDS Relief</td>
</tr>
<tr>
<td>PPP</td>
<td>public-private partnerships</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>research and development</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>TDR</td>
<td>Special Programme for Research and Training in Tropical Diseases</td>
</tr>
<tr>
<td>UNAIDS</td>
<td>United Nations Programme on HIV/AIDS</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
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<td>WHO</td>
<td>World Health Organization</td>
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</table>
Executive summary

This report presents an overview of in vitro diagnostic (IVD) device technology transfer and local production of diagnostic tests for developing countries. The report identifies needs and analyses trends in the local production of diagnostics and related technology transfer. A series of recommendations are made. The objective is to assist the World Health Organization (WHO) in its support for Member States in implementing the global strategy and plan of action on public health innovation and intellectual property, with particular reference to the promotion of capacity building for local production in developing countries.

High-quality diagnostic technologies are available for infectious diseases in most developed countries, but they are neither accessible nor affordable in developing countries, where disease burdens are high. Evidence-based treatment using diagnostic test results is needed to replace syndromic management, which is often ineffective and increases the risk of development of antibiotic resistance. Although the long-term solution is to build capacity for diagnostic innovation in developing countries, technology transfer and local production can be an effective and sustainable strategy by which to increase access to diagnostic tests. This report examines current models of technology transfer and local production, identifies successes, failures, challenges and opportunities, and presents recommendations with a view to developing better models for the future. The main findings are:

1. Developing countries have variable capacity for diagnostic research and development (R&D) and local production of diagnostics. Manufacture in the non-industrialized world is most often undertaken in countries with large domestic markets and emerging economies such as China, India and Brazil.

2. There are several models by which technology transfer for local production can be accomplished. These range from the transfer of R&D know-how to enable local product development to merely partnering with a company in the developing world to manufacture a product, without increasing local capacity for R&D.

3. Successful partnerships have involved small and medium-sized companies, multinational companies, non-profit-making organizations and the public sector. The most successful example to date includes the transfer of a novel technology from an IVD company registered in the developed world to a non-profit-making public institution in the developing world. The agreement not only permits local production of tests based on this technology but also allows further R&D using the novel technology to produce tests for diseases prevalent in the developing country.

4. In spite of these successes, many obstacles to technology transfer and local production remain. They include:
• lack of financial investment for development of diagnostics, a situation compounded by a lack of market knowledge, where analysis to map out market size and demand, desired product specification and pricing is badly needed;
• lack of commitment of developing country governments to purchase locally produced goods;
• unclear means to enforce intellectual property rights;
• lack of clear pathway and mechanisms for taking R&D products to market;
• restricted freedom to operate, where non-profit-making manufacturers are not permitted to engage with the commercial sector;
• lack of local expertise in quality-assured manufacture, packaging or distribution;
• lack of transparency and clarity of standards in regulatory approval mechanisms and lengthy approval processes, a situation compounded by the lack of regional harmonization;
• lack of quality standards in diagnostic test evaluation and lack of access to quality control/quality assurance materials, allowing proliferation of poor quality tests;
• rationalization of companies following mergers and acquisitions;
• need for prequalification/evaluation of products before entering the market;
• competition from established suppliers offering cheap imports, a wider range of goods or inducements to secure contracts;
• local markets that are unable support manufacture on a scale that is cost efficient.

5. Opportunities to increase technology transfer include:

• increased political will and recognition of the value of diagnostics at a national and international level;
• increased funding and networking initiatives through product development partnerships; however, these remain focused largely on research rather than on building capacity for manufacturing, and access to finance remains the foremost challenge for test developers;
• interest in personalized medicine by pharmaceutical companies and emergence of new point-of-care technology suited to resource-poor environments;
• vibrant biotechnology sector in some developing countries that can act as hubs for regional initiatives.

Based on the findings above, a number of steps must be taken to promote, support and develop initiatives and mechanisms for enhancing technology transfer and local production of diagnostics (Table 1).
Table 1 Recommendations for enhanced technology transfer and local production of diagnostic technology

<table>
<thead>
<tr>
<th>Promote</th>
<th>Support</th>
<th>Develop</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advocate the importance and value of diagnostics to the pharmaceutical industry, and national and international stakeholders</td>
<td>Provide guidance on required test specifications for Developing countries for test developers</td>
<td>Develop new business models and approaches to financing and marketing of diagnostics</td>
</tr>
<tr>
<td>Analyse the developing world market and provide data to test developers, potential investors and local stakeholders</td>
<td>Provide critical pathway for successful technology transfer and examples of best practice</td>
<td>Explore novel initiatives by which to share and exploit intellectual property</td>
</tr>
<tr>
<td>Enhance capacity within developing countries to adopt new diagnostic and manufacturing technology</td>
<td>Provide advice and training on protecting intellectual property. Collate and distribute information on patents and where they apply</td>
<td>Establish a global association for manufacturers of diagnostic tests</td>
</tr>
<tr>
<td>Recognize excellence in diagnostic expertise and establish a professional career pathway in diagnostics R&amp;D</td>
<td>Support training to enhance capacity for GLP/ISO manufacturing in Developing countries</td>
<td>Establish a global diagnostics forum for information sharing, enable debate and encourage collaboration and harmonization</td>
</tr>
<tr>
<td>Support capacity building to increase the number of stringent regulatory authorities in developing countries</td>
<td></td>
<td>Develop a health technology assessment model for countries to determine whether new technologies address their Public Health needs</td>
</tr>
</tbody>
</table>

GLP, good laboratory practice; ISO, International Organization for Standardization.
1. Background and context

In May 2008 and 2009 the World Health Assembly adopted Resolutions WHA61.21 and WHA62.16 on the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPA-PHI). This is a landmark agreement, as it aims to improve treatment for poverty-related and neglected diseases disproportionately affecting developing countries by stimulating innovation to find new products for these diseases, and by improving availability, affordability, access and acceptability of existing products.

The plan incorporates eight elements:

1. Prioritize research and development (R&D) needs.
2. Promote R&D.
3. Build and improve innovative capacity.
4. Transfer of technology.
5. Application and management of intellectual property to contribute to innovation and promote public health.
6. Improve delivery and access.
7. Promote sustainable financing mechanisms.
8. Establish and monitor reporting systems.

Among other areas, the global strategy highlights the need to build and improve innovative capacity in developing countries (element 3) and to facilitate the transfer of health-related technology (element 4), including pharmaceuticals, vaccines and diagnostics. Technology transfer is the sharing of knowledge from those that know with those that do not. It is shaped by the environment with respect to local capacity, ownership of intellectual property, availability of finance and other factors.

This report makes a number of recommendations. These are focused mainly on the role that the World Health Organization (WHO) can take, working in partnership with others, in terms of implementing the GSPA-PHI with respect to the transfer of technology and local production of diagnostics in developing countries.

In vitro diagnostic (IVD) devices are tests that can detect diseases, conditions or infections. They are used at all levels of the health-care system and range in complexity from sophisticated computer-controlled analytical systems to simple dipstick technologies. IVD devices inform decisions regarding appropriate care and management of patients. For many conditions, including human immunodeficiency virus (HIV) infection, access to treatment is dependent on prior access to the appropriate diagnostic test.

To be useful, diagnostic tests must be accurate, simple and affordable for the population for which they are intended. They must also provide a result in time to institute effective treatment. Early diagnosis and treatment of an infection
may have an important role in interrupting transmission of the infection agent. In a broader context, diagnostic tests may be useful for:

- patient management, especially when clinical presentation is nonspecific;
- detection of asymptomatic infections;
- surveillance;
- situation analysis, including detection of previous infections;
- evaluation of effectiveness of interventions, including certification of elimination;
- detection of drug resistance, by detecting treatment failures.

High-quality tests for infectious diseases are readily available in most developed countries; however, the situation is very different in developing countries, where the cost of imported IVD technology is frequently too high for the public sector. As a result, diagnostic tests are not affordable by those vulnerable populations with the highest burden of disease. IVDs that are available in the poorest countries are often the result of a dependency on international donors engaged in disease-specific initiatives. There is a strategic tension between societal needs and corporate perspectives on the supply of diagnostic devices. The perceived lack of a commercial market for diagnostics for neglected diseases has contributed to the lack of available tests in developing countries. There are also tensions between affordability and access and sustained local production, where imported tests may have a lower economic cost due to donations or special procurement arrangements, discouraging local investments in the development and manufacture of such products. The failure of traditional market-led business models to provide diagnostic tools for developing countries had led to recognition that alternative means of production should be considered.

Transfer of health-related technologies has been credited with the potential to build health security, increase reliability of supply, decrease reliance on imports, lead to lower prices, and encourage development and production that is more suitable for local health needs. Thus, implementation of the global strategy regarding innovation and local production may contribute to a sustainable and long-term solution to the persistent challenge of access to health care for the most vulnerable populations. Implementation of GSPA-PHI has led to a number of initiatives, including the consideration of issues relating to technology transfer and the manufacture of diagnostic tests in developing countries. WHO, in partnership with the London School of Hygiene & Tropical Medicine, and with funding by the European Union (EU), undertook a project relating to technology transfer and local production to inform future initiatives for the improved access to diagnostics in the developing world. This report is the result of that project. It encompasses an overview and analysis of the current landscape of R&D and production of IVDs for developing countries. It reviews opportunities and makes recommendations for more effective technology transfer and local production of diagnostics to improve access to diagnostic tests in developing countries.
2. Objectives and methodology

Technology transfer is the sharing of knowledge from those who own the know-how to those who do not. It is shaped by many factors, including the capacity of recipient countries to absorb the knowledge and translate the know-how into the manufacture of a diagnostic test. Technology transfer and local production are often motivated by cheaper production costs and easier penetration into emerging markets. In this report, the term “developing countries” includes the emerging economies of China, India and Brazil, and all other countries classified as low- or middle-income according to the World Bank statistics. It is acknowledged that this gives a very broad range of countries with very different country profiles and requirements.

2.1 Project objectives

1. Conduct a survey of technology transfer and local production of diagnostics for developing countries.

2. Analyse the global trend of technology transfer and local production for diagnostics in the context of improved access to diagnostic tools for infectious diseases with specific country examples.

3. Conduct stakeholder interviews and focus group discussions on access of diagnostics in developing countries.

4. Collate and synthesize all data into a summary technical report with specific recommendations on the way forward.

2.2 Project activities

1. Assessment of the global diagnostics market and its relevance to developing countries.

2. Survey of technology transfer and local production of diagnostics in developing countries.

3. Assessment of opportunities and barriers to technology transfer and local production of diagnostics.

4. Stakeholder consultation with regard to technology transfer and access to diagnostics by vulnerable populations.

5. Compilation of evidence and stakeholder opinion on technology transfer and local production.

6. Generation of recommendations for improved access to diagnostic tests through technology transfer for local innovation and production.
2.3 Methodology

Evidence was gathered and collated through a combination of desk research and interviews. Stakeholders consulted included public health officials, procurement officers, regulatory officers, public- and private-sector test developers, test evaluators, patient representatives, clinical personal, diagnostic laboratory personnel, economists, health policy experts and representatives of manufacturers’ associations. Countries represented included Brazil, Cameroon, China, Germany, Ghana, India, Italy, the Netherlands, Nigeria, South Africa, Thailand, Uganda, the United Kingdom of Great Britain and Northern Ireland, the United Republic of Tanzania, the United States of America and Zambia.

A workshop, Dialogue on Technology Transfer for Local Manufacturing Capacity of Diagnostics, was held in Dionne les Bains, France in October 2010. Over 30 experts participated in discussions on technology transfer for IVD for developing countries. (See Annex I for a list of attendees.)

Case studies were undertaken to illustrate the challenges and to exemplify strategies for technology transfer and local production. Successful and unsuccessful initiatives are presented to illustrate the opportunities and obstacles for sustainable local production.

3. The diagnostics landscape

In vitro diagnostic devices are tests that can detect diseases, conditions or infections. They are used at all levels of the health-care system and range from self-test devices for use in the home to sophisticated high-throughput computer-controlled analysers. Commercial kits are available for many but not all infectious diseases. In addition to purchasing ready-made devices, laboratories can also assemble and use their own in-house tests. IVD devices differ from other medical products such as drugs and vaccines in a number of ways; perhaps one of the most significant is the lack of a stringent regulatory control regarding their effectiveness.

3.1 In vitro diagnostics commercial market

The field of diagnostics is very different from that of pharmaceuticals and vaccines. It has a much smaller market than drugs. Diagnostics and diagnostics research are often undervalued. The Lewin Report on the Value of Diagnostics noted that although diagnostics comprise less than 5% of hospital costs and about 1.6% of all United States Medicare costs, their findings influence 60–70% of health-care decision-making (Lewin Group, 2005). In the developing world, diagnostics is often a negligible proportion of health-care spending. A WHO study in Malawi showed that only 6% of health expenditures at a district hospital is spent on diagnosis (WHO, 2003).

The magnitude of the global IVD market and predictions regarding future trends are the subject of commercial speculation. Estimates of market value
vary according to the evidence used to compile the information, and it is not always possible to identify the source or verify the accuracy of data published by commercial organisations. Nonetheless there is general agreement that the market is expanding and that there are commercial opportunities in the emerging economies of Asia and Latin America. Economic and political pressure to minimize health-care expenditure is driving demand for high-throughput automated diagnostic platforms placed in large centralized laboratory services. A second area of expansion is in simple rapid devices that can be used close to the patient in primary health clinics and hospital wards, reducing the need for referral to laboratory-based services (Peeling & Mabey, 2010). A new model of commercial health management is emerging, with multinational companies providing complete diagnostic service packages to both public- and private-sector clinics and hospitals. These companies have enormous bulk procurement contracts with IVD companies and can have significant influence on market trends. This innovation is not confined to industrialized countries. Transnational health-care delivery companies are expanding to countries such as Brazil, India and South Africa.

Another feature of the diagnostics market that is different from medicine and vaccines is the short lifespan of products. Improved devices and new replacement technologies are frequently introduced. This is illustrated by the introduction of new molecular technologies for screening for drug-resistant tuberculosis (TB), which are replacing the slow, cumbersome, culture-based tests that require stringent microbiological safety precautions. Data from the South African National Health Laboratory Service (NHLS) are shown in Table 2 and Figure 1 (Erasmus et al., 2010). The mycobacteria growth indicator tube (MGIT) culture-based system was used before the introduction of a new molecular test, the line probe assay, in 2006–2007. With the implementation of the more rapid molecular test, there was a subsequent drop in the use of culture-based tests. A new technology, the Xpert MTB/RIF (Cepheid, Sunnyvale, CA, United States) test, also a molecular test, is now set to replace the Line Probe Assay. The Xpert test is much simpler to perform than the line probe assay and South Africa is planning to purchase a number of instruments to allow rapid diagnosis and screening for drug resistance in diagnostic centres, where use of the line probe assay will then be restricted to confirmatory testing of people found positive for resistance by the Xpert test.
Revenues during 2009 were US$ 1523 million, US$ 674 million and US$ 402 million. According to a report produced by Global Business Intelligence (GBI) Research, the global market for IVD during 2009 was estimated to be worth US$ 37 billion (GBI Research, 2010). The market is not distributed evenly and, not surprisingly, is dominated by wealthy countries. Increased expenditure on health in emerging economies such as Brazil, China and India and an anticipated increase in demand for health care from ageing populations is fuelling growth of the IVD market. The market data available for developing countries are limited in scope, but estimates for China, Brazil and India suggest revenues during 2009 were US$ 1523 million, US$ 674 million and US$ 402 million.

Table 2 Number of Mycobacterium tuberculosis drug susceptibility tests performed by a newly introduced method and the traditional method at NHLS, South Africa, by year

<table>
<thead>
<tr>
<th>Year</th>
<th>Molecular test (line probe assay)</th>
<th>Culture-based test (MGIT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>–</td>
<td>34 564</td>
</tr>
<tr>
<td>2005</td>
<td>1</td>
<td>36 903</td>
</tr>
<tr>
<td>2006</td>
<td>5</td>
<td>48 183</td>
</tr>
<tr>
<td>2007</td>
<td>5963</td>
<td>65 809</td>
</tr>
<tr>
<td>2008</td>
<td>23 128</td>
<td>60 147</td>
</tr>
<tr>
<td>2009</td>
<td>61 575</td>
<td>40 204</td>
</tr>
<tr>
<td>2010*</td>
<td>65 190</td>
<td>22 840</td>
</tr>
</tbody>
</table>

*Projected number of tests (full data not available).

Figure 1 Number of Mycobacterium tuberculosis drug susceptibility tests performed at NHLS, South Africa, by year

According to a report produced by Global Business Intelligence (GBI) Research, the global market for IVD during 2009 was estimated to be worth US$ 37 billion (GBI Research, 2010). The market is not distributed evenly and, not surprisingly, is dominated by wealthy countries. Increased expenditure on health in emerging economies such as Brazil, China and India and an anticipated increase in demand for health care from ageing populations is fuelling growth of the IVD market. The market data available for developing countries are limited in scope, but estimates for China, Brazil and India suggest revenues during 2009 were US$ 1523 million, US$ 674 million and US$ 402 million.
It can be seen that although 50% of disease in developing countries is attributable to communicable diseases, the infectious immunology and microbiological culture sectors when combined represent less than 20% of the global diagnostics market. As illustrated in Figure 5, most revenue attributed to immunological tests for infectious disease is for the detection

Source: Data from GBI Research (2010).

**Figure 2** Estimated share of global IVD markets for selected countries, by revenue

Source: Data from GBI Research (2010).

**Figure 3** Estimated share of global IVD markets for selected countries, by revenue (US$)

Source: Data from GBI Research (2010).

The relative values of the various IVD product groups are presented in Figure 4. It can be seen that although 50% of disease in developing countries is attributable to communicable diseases, the infectious immunology and microbiological culture sectors when combined represent less than 20% of the global diagnostics market. As illustrated in Figure 5, most revenue attributed to immunological tests for infectious disease is for the detection
of viral infections. Bacteriology represents the main culture activity (Figure 6); culture of mycobacteria, including TB, had an estimated global value of US$ 574.6 million during 2009.

**Figure 4 Global IVD revenue, by diagnostic category**

Source: Data from GBI Research (2010).

**Figure 5 Immunological tests sold for infectious diseases**

Source: Data from GBI Research (2010).
3.2 Developing country market structure

In developing countries, health care is sought from many sources: the public (government) sector, private practitioners, nongovernmental organizations (NGOs) and traditional healers (Case & Menendez, 2005; Uzochukwu & Onwujekwe, 2004). There is cross-referral of patients for diagnostic services, with some commissioning of private laboratories by the public sector and some use of the public sector by private practitioners and NGOs. Disparities in access between rural and urban populations are frequent: the level and quality of care experienced by these populations can vary widely, from primitive clinical outposts to large centralized laboratories. Also, reduced access may be experienced by women and other vulnerable groups due to economic or social disadvantage. For patients not covered by insurance schemes, diagnostic tests are rarely free at the point of delivery and often come with significant fees. In countries such as South Africa and Brazil the public sector is the major provider of primary health-care services, but in other settings diagnosis is more frequently sought from the nongovernmental sector. The pattern of health-seeking behaviour varies within countries and is influenced by the accessibility and perceived quality of local services (Sudha et al., 2003). Examples of diagnostic services in developing countries are given in Table 3.

Emerging economies such as Brazil, India and South Africa provide established and growing markets for the private health sector, and multinational companies have established a presence in these countries through partnership or by acquisition of local diagnostic companies. In emerging economies such as China and Brazil, the burden of disease is changing where rising living standards and an ageing population are resulting in increased demand for diagnosis and management of chronic diseases and cancers (MarketsandMarkets, 2010). Revenue from commercial IVD products in these countries has a similar distribution to that in the global market. A breakdown of the diagnostic market in South Africa is presented in Figure 7.
In less developed countries, private diagnostic laboratories have been established in response to the low level of service available from the public sector and to reduce the need to travel abroad for medical care. In addition to procurement from commercial agencies, developing countries may also access IVD at preferential prices or through international initiatives such as UNITAID, the Global Fund to Fight AIDS, TB and Malaria, or the United States President’s Emergency Plan for AIDS Relief (PEPFAR). However, these initiatives are frequently restricted to specific disease-control programmes such as those for HIV, TB and malaria, and countries that they support. A further concern is that these short-term funding mechanisms cannot be considered sustainable.

### Table 3 Examples of diagnostic services in developing countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Diagnostic service provision</th>
</tr>
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<tbody>
<tr>
<td>Brazil</td>
<td>There are mixed public and private services, with an estimate of nearly 8000 clinical laboratories. Brazil has universal health care and the public unified health system coexists with the private health-care system. The public sector is estimated to purchase 60% of the IVD market. There are 400 million diagnostic tests annually in the public sectors. Chains of private laboratories and some large referral centres provide high-throughput screening in urban centres. The Immunobiological Technology Institute (Bio-Manguinhos) was established in 1976 as the technical-scientific unit of the Oswaldo Cruz Foundation (Fiocruz), which produces and develops vaccines and immunobiological products to respond to public health demands in Brazil and in the region. It currently produces more than 3 million reagents for diagnostics tests each year.</td>
</tr>
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</table>

Continues...
Country Diagnostic service provision

South Africa There are mixed public and private laboratories. The major provider is NHLS, a non-profit-making organization with a national network of 265 pathology laboratories. This provides laboratory diagnostic services (e.g. surveillance studies) to the Department of Health, provincial and district hospitals, primary health-care clinics and other state institutions (e.g. prisons). It also offers a referral diagnostic service to private-sector health-care providers. It is the main purchaser of commercial IVDs but it also uses in-house tests, including some nucleic acid amplification tests.

Private laboratories provide a service to the private health clinics and hospitals and for occupational health screening such as in the mining industry.

India There are mixed public and private laboratories. Estimates suggest over 1 million patients per day are tested in approximately 30,000 laboratories. The nongovernmental sector is playing an increasing role, with the establishment of public–private partnerships. In some urban slums an estimated 70% of outpatients attend private clinics.

Zambia The Ministry of Health is the major provider. It is heavily dependent on donor funding, and shortages of trained personnel and reagents are common. There are private laboratories in the capital Lusaka and serving the mining industry in the copper belt. NGOs provide diagnostics for HIV and in some cases TB or malaria. Recent deterioration of services was experienced following suspension of donor funds because of corruption.

China There are mixed public and private laboratories. The central Government is in the process of introducing a basic health insurance scheme, but in the meantime clinics and hospitals depend on fees charged to patients for physician time, diagnostic services and drugs to stay in business. China has prioritized HIV, TB, hepatitis B and schistosomiasis as top infectious disease priorities in health and diagnostic services, and drugs for these diseases should be available free of charge at Government clinics. However, many people attend private clinics and hospitals in preference to public facilities and pay out of pocket if they do not have health insurance through their employer.

3.3 Demand-side priorities and gaps

Global health priorities have been established through the Millennium Development Goals. Detection of communicable diseases remains a priority, not only to reduce individual morbidity and mortality but also – in the case of sexually transmitted infections and respiratory infections – to prevent onward transmission. Whereas in some countries health care for HIV, TB and malaria is funded by the Global Fund to Fight AIDS, TB and Malaria, diagnostics for other diseases remain woefully underfunded (Mabey et al., 2004). The majority of populations living in least developed countries have limited or poor access to diagnostic services. This may be due to the cost or because they live a long distance from health-care facilities. Lack of access is partly due to inadequate service provision, where tests that are theoretically available are not delivered.
because of poorly functioning health-care systems. There may also be a lack of availability, either because the tests are not imported or because appropriate tests for the disease do not exist. Similarly some vulnerable populations do not seek diagnostic services because of issues such as stigma or social exclusion.

The following factors have been identified as factors contributing to poor access to diagnosis:

- **Access issues:**
  - lack of laboratory facilities;
  - lack of trained personnel;
  - long distance to nearest laboratory;
  - high cost to patient of seeking medical care;
  - poor awareness of the population of disease symptoms and of the diagnostic opportunities, leading to low health-seeking behaviour;
  - tests not available due to lack of investment in R&D of new diagnostics.

- **Quality issues:**
  - poor-quality tests;
  - test robustness in varying environmental conditions;
  - difficulties in repairing equipment;
  - tests not appropriate for population and unclear product guidelines/specifications for specific disease and population.

- **Implementation issues:**
  - poor implementation of diagnostics into health-care system;
  - supply chain problems (stockouts, customs duties, distribution networks);
  - lack of human resources and appropriate training.

In the absence of diagnostic services, WHO promotes the use of a syndromic approach to management of infectious diseases where presumptive treatment is given for all major causes of the syndrome. For example, before 2009, the Integrated Management of Childhood Illness (IMCI) guidelines, developed by WHO and the United Nations Children’s Fund (UNICEF), recommended that presumptive treatment for malaria be given to all children presenting with fever in a malaria-endemic area. This approach has low specificity and increases the risk of development of drug resistance. The emergence of chloroquine resistance resulted in the use of rapid tests for malaria. These diagnostic tests demonstrated that malaria is not as common as previously thought and that children given presumptive treatment for malaria often die of bacterial or viral infections that were never diagnosed. The need for evidence-based management of infectious diseases, particularly in resource-poor settings, drives current investments in point-of-care diagnostics to improve global health (Table 4).
Table 4  Estimated potential impact of rapid point-of-care tests

<table>
<thead>
<tr>
<th>Disease</th>
<th>Population</th>
<th>Sensitivity/ specificity (%)</th>
<th>Potential impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lower respiratory infection</td>
<td>Children under 5 years</td>
<td>95/85</td>
<td>Saves about 405 000 lives</td>
</tr>
<tr>
<td>HIV</td>
<td>Infants under 12 months</td>
<td>90/90</td>
<td>Saves 2.5 million DALYs if 100% access to treatment</td>
</tr>
<tr>
<td>Malaria</td>
<td>Children under 5 years</td>
<td>90/90</td>
<td>Saves 2.2 million DALYs and prevents 447 million unnecessary treatments</td>
</tr>
<tr>
<td>TB</td>
<td>Symptomatic</td>
<td>85/97</td>
<td>Saves about 400 000 lives</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Prenatal</td>
<td>86/72</td>
<td>Saves 201 000 DALYs and averts 215 000 stillbirths</td>
</tr>
<tr>
<td>Chlamydia and gonorrhoea</td>
<td>Sex workers</td>
<td>85/90</td>
<td>Saves about 4 million DALYs, averts 16.5 million new cases and prevents 212 000 cases of HIV</td>
</tr>
</tbody>
</table>

DALY, disability-adjusted life-year.
Source: Urdea et al. (2006).

Diagnosis of TB has been singled out as in need of urgent improvement because current case detection rates fall well short of the target set by WHO to control the disease (McNerney & Daley, 2011). Laboratory-based tests used in industrialized countries have proved difficult to implement in developing countries with poor laboratory infrastructure (Anthony et al., 2009). It has been estimated that a widely implemented diagnostic test with a sensitivity of 85% could reduce deaths from TB by nearly 400 000 each year if used to initiate treatment (Keeler et al., 2006).

An example of technology that is not affordable in counties with the greatest need is the Xpert MTB/RIF assay, which tests for TB in sputum and simultaneously detects resistance to the major anti-tuberculosis drug rifampicin (Helb et al., 2010). The test represents a major breakthrough in TB diagnosis, but unfortunately the high cost will limit its application in countries with a high burden TB (McNerney & Daley, 2011).

Health priorities vary across countries and regions and are related to local demographic and geographical factors (Table 5).
<table>
<thead>
<tr>
<th>Priorities</th>
<th>Gaps</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brazil</strong></td>
<td>Disparities in need and access across regions, reflecting local climate, terrain and poverty levels</td>
</tr>
<tr>
<td>Infectious diseases: lower respiratory tract infections (including TB), malaria, HIV, Chagas disease, dengue, diarrhoeal diseases</td>
<td>Rapid tests for some diseases not available</td>
</tr>
<tr>
<td><strong>South Africa</strong></td>
<td>Disparity of service provision in urban and rural areas; reduced access due to economic, social and geographical factors</td>
</tr>
<tr>
<td>Current national health priorities are HIV/AIDS and TB. The HIV prevalence rate is approximately 10.6% (17% for people aged 15–49 years), with about 5.21 million people living with HIV (Statistics South Africa, 2009). HIV/AIDS is the leading cause of death (28.8%). The estimated TB incidence was 476 732 in 2008 (WHO, 2009). Emergence of drug-resistant forms of TB and HIV has worsened the situation</td>
<td>Diagnostic delay in people with TB – accurate, rapid point-of-care tests not available; need earlier diagnosis of TB in people with HIV coinfection to prevent rapid disease progression</td>
</tr>
<tr>
<td>Other infections of note include sexually transmitted infections, upper respiratory tract infections and, in some regions, malaria</td>
<td></td>
</tr>
<tr>
<td><strong>India</strong></td>
<td>Limited access due to economic, social and geographical factors</td>
</tr>
<tr>
<td>Lower respiratory tract infections, TB and diarrhoeal diseases</td>
<td>Woman and tribal groups marginalized</td>
</tr>
<tr>
<td>In some regions parasitic diseases such as malaria and leishmaniasis</td>
<td>Accurate rapid tests for some diseases not available</td>
</tr>
<tr>
<td>HIV/AIDS has been added to the list of priority diseases</td>
<td></td>
</tr>
<tr>
<td>High burden of chronic disease such as diabetes</td>
<td></td>
</tr>
<tr>
<td><strong>China</strong></td>
<td>Disparity of service provision in urban and rural areas</td>
</tr>
<tr>
<td>Lower respiratory tract infections, TB, HIV prevention, hepatitis B, sexually transmitted infections, schistosomiasis and other parasitic diseases</td>
<td>Migrant workers and other vulnerable populations have reduced access due to economic and social factors</td>
</tr>
<tr>
<td>China is on course to eliminate malaria, leprosy and schistosomiasis and would need tests of high sensitivity and specificity to certify elimination</td>
<td>Diagnostic delay in people with TB – accurate, rapid point-of-care tests not available; need earlier diagnosis of TB to control epidemic</td>
</tr>
</tbody>
</table>

There are few hard data on the unmet need for diagnostic tests in developing countries or on the potential market opportunities.
3.4 Supply-side landscape

3.4.1 Diagnostic test manufacturers

Manufacturers of diagnostic tests range in size and scope, from large multinational corporations to small local companies employing a handful of people. A number of non-profit-making organizations and product development partnerships are also involved in the manufacture of diagnostic tests. The market is less dominated by large multinational corporations than are other pharmaceutical sectors. During 2008 small companies took an estimated 42% share of global revenues. Four companies (F. Hoffmann-La Roche Ltd, Siemens Medical Solutions, Abbott Laboratories and Beckman Coulter) had an estimated combined global market share of 44% (Figure 8). However, multinational companies had a greater share of the revenue from diagnostic products for infectious disease immunology (Figure 9).

Figure 8 Estimated global market share by revenue, 2008. (Total revenue: US$ 35 655 million)

Source: Data from GBI Research (2010).
Figure 9 Estimated infectious disease immunology global IVD market share by revenue, 2008. (Total revenue US$ 4357 million.)

It should be noted that there has been consolidation of IVD companies in recent years, with a number of mergers and acquisitions, a process that is continuing. Thus, as the number of companies is shrinking, the overall share of the market by large multinational companies is increasing due to the acquisition of local manufacturers and distributors. One company has made over 30 acquisitions in the past 5 years, including companies in Brazil, China, India, South Africa and the Republic of Korea.

There is no global or international diagnostics manufacturers’ association equivalent to the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), which has a biannual general assembly and a code of conduct for its members. The formation of a global or international diagnostics manufacturers’ association would give the diagnostic industry a single voice to advocate issues important to its members and would provide a forum with which governments and international agencies could work to institute quality standards for the industry.

3.4.2 Product development partnerships

The most significant non-profit-making organization involved in the manufacture of IVD is the Oswaldo Cruz Foundation (Fiocruz) in Brazil, which supplies a range of products to the public programmes of the General Coordination of Public Health Laboratories of the Health Surveillance Secretariat, the National Program on Sexually Transmitted Diseases and Aids and epidemiological surveillance programmes. Other non-profit-making organization involved are the Foundation for Innovative New Diagnostics (FIND; Geneva, Switzerland) and the Program for Appropriate Technology in Health (PATH; Seattle, WA, United States). FIND and PATH are focused more on
R&D and less on manufacturing of tests, but they do address problems with supply through preferential pricing structures (Box 1).

**Box 1 PATH and FIND**

PATH is an international non-profit-making organization based in the United States that aims to deliver health technologies designed for low-resource settings through working with local communities and in partnership with the commercial sector. Its work on diagnostic tools focuses on low-cost point-of-care IVDs. PATH works with partners in developing countries to optimize and evaluate new tests. Successful products have included rapid tests for HIV, malaria and syphilis (PATH, 2005). In addition to product development, it undertakes technology transfer to developing countries through nonexclusive licensing to private-sector diagnostic manufacturers.

FIND is a non-profit-making organization based in Switzerland. Its mission is to drive the development and implementation of accurate and affordable diagnostic tests that are appropriate to patient care in low-resource settings. FIND focuses on three diseases: TB, sleeping sickness and malaria. It works through partnership with commercial companies on technologies already used in industrialized counties and on the development of new tests. To date, FIND’s manufacturing partners are companies based in Europe, the United States and Japan. Following successful product evaluation, FIND negotiates reduced pricing schemes for public-sector health providers in disease-endemic countries. Its products so far are laboratory-based and it has embarked on a programme of laboratory capacity building in developing countries to enable successful implementation.

3.5 Regulatory environment

IVDs are not controlled to the same degree as other medical commodities such as pharmaceuticals and vaccines. The United States Food and Drug Administration (FDA) requires that IVDs that are sold and used in the United States only must be registered and meet specified standards regarding good manufacturing practice (GMP), quality, labelling, safety, effectiveness, and data on their performance in defined patient groups. The expense and logistical cost of seeking FDA approval is high, at approximately US$ 2 million; hence, companies with commercial products not intended for the United States market seldom submit these products for FDA assessment. European regulatory processes vary across different countries.

The FDA has three levels of classification of devices. Regulation includes lot release criteria, design controls, monitoring, reviews of standard operating procedures, bioresearch inspections of clinical sites and data collection. Practices are stringent. Applicants have to test their product using specimens from the Center for Biologics Evaluation & Research or the Centers for Disease Control. Reporting of incidences is enforced, and health hazard evaluations must be performed, leading to product recall if necessary. The FDA has no jurisdiction outside the United States, and its performance and stability requirements
may be very different from those required in other settings, especially tropical climates. The FDA is expanding its global base, with international offices being introduced gradually. Some tests are required to demonstrate efficacy in non-United States conditions – for example, malaria tests need to work in high temperatures and in the presence of other *Plasmodium* species.

For products made in the United States for export, the FDA issues a certificate of export, which is sometimes misrepresented by sales staff in developing country companies as FDA approval.

Europe uses the Conformité européenne (European conformity; CE) marking process, which is not concerned with quality of the product but addresses GMP. The CE mark does not require monitoring or surveillance. A system based on GMP cannot guarantee good performance in a product, but can guarantee only manufacturing quality, consistency and safety. All products for sale in the European Union region are required to display the CE mark, which certifies that a product has met EU consumer safety, health or environmental requirements. CE marking does not relate to the effectiveness of the product or its ability to correctly detect disease, and it is generally not considered equivalent to FDA approval.

Japan uses levels of regulation like those of the United States, but regulation does not exist for diagnostics and is seen only as a formality. There is no monitoring of quality after licensing has been set up.

Many other countries have no regulatory system for diagnostics and no means of assessing the quality of tests, whether imported or manufactured locally. A survey conducted by WHO/TDR in 2001–2002 revealed that few developing countries have bodies that regulate IVDs or monitor the diagnostics industry (Figure 10). Whereas some control is exercised over the screening tests used in blood banks, few checks are made on the efficacy of tests for the diagnostic laboratory. The lack of regulation has allowed a large array of poor-performing diagnostics on to the market. These low-quality tests are generally sold at a very low price, with little to no guarantee of their results. They are a particular concern in the private sector, where they are sold openly, sometimes with misleading or inaccurate performance data. The lack of regulation is a serious concern that has been discussed in a number of fora (Academy of Medical Sciences, 2009). A summary of regulatory approval mechanisms is presented in Table 6.
In summary, there are three levels to existing diagnostics regulation processes globally:

- No regulation at all.
- Registration with a regulatory agency required to sell a product, but requiring no evaluation or information on the quality of the product.
- Registration and evaluation – this is required for a few but not all products (e.g. HIV tests).

There is no international standard that manufacturers must meet. Some companies choose to follow the GMP ISO guidelines, but others do not think this is necessary. There is no means of enforcement.

There is no harmonization of requirements for registration. If a company wants to sell its product abroad, the company has to acquire the licensing certificate from each country its wishes to sell in and undergo the whole registration process separately for each country, which discourages global distribution.

3.5.1 Problems with existing regulatory systems

- Approval process is not transparent and is lengthy.
- No means of enforcement of standards.
- No harmonization between different systems.
- No single point of entry for regulatory approval in multiple countries.
- Requirements are not always applicable in developing countries.
• Requirements do not always measure or reflect quality or efficacy.
• Staffing levels are often inadequate for carrying out inspections or monitoring.
• There is a paucity of information on existing regulatory practices to assess the current situation accurately.
• Availability of diagnostics in smaller countries is problematic, as diagnostic companies have limited resources to conduct trials in every country and would rarely invest resources to seek approval.

3.5.2 Global Harmonization Task Force (GHTF) for diagnostics regulation

The Global Harmonization Task Force (GHTF) was established in 2002 and there is a specific group for IVDs. However, these groups are making very slow progress. Environmental scanning is needed to map the regulation of IVDs and assess the extent of disparity between countries.

The Asia Harmonization Working Party (AHWP) has an agreed regulation system of medical devices and has in recent years established a working group (WG01A) involving 20 countries to specifically look at the market approval of IVDs. The aim of AHWP is to develop one agreed standard for a regulatory system for IVDs and to provide a template for countries to tailor to their own particular requirements.

Lots of work is carried out in China with GHTF and AHWP, involving many multinational companies. Smaller companies, however, have no real representation in the groups and therefore little access to the regulatory guidelines produced. The regulations need to be made transparent for all.

Table 6 Regulatory and approval mechanisms

<table>
<thead>
<tr>
<th>Agency</th>
<th>Scope</th>
<th>Jurisdiction</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA (United States)</td>
<td>Rigorous testing to establish performance in defined target population</td>
<td>Required for United States market, but high cost deters application</td>
</tr>
<tr>
<td>CE mark (Europe)</td>
<td>Marker for quality but not a guide on performance</td>
<td>Required for European market</td>
</tr>
<tr>
<td>Country review</td>
<td>Review by national agency before adoption by public health sector</td>
<td>May involve testing in national laboratory; widely ignored by private sector</td>
</tr>
</tbody>
</table>

Examples of regulatory processes in developing countries are presented in Table 7. In practice, although most countries require registration of products for a fee, few demand evidence of their accuracy or of their performance in the local population. Public sector procurement is guided by WHO recommendations, where available. Controls and monitoring are soon to be increased in South-East Asia where there are moves by the Association of South-East Asian Nations (ASEAN: Indonesia, Singapore, Malaysia, the Philippines, Thailand, Brunei, Cambodia, Viet Nam, the Lao People’s Democratic Republic and Myanmar)
to harmonize regulation of medical devices. China has also increased the regulatory requirements for IVDs for its domestic market.

It should be noted that not all countries have equal access to the international diagnostics market, and restrictions apply to the export of goods from the United States to Cuba, Iran, the Libyan Arab Jamahiriya, the Democratic People’s Republic of Korea, Sudan and the Syrian Arabic Republic.

**Table 7 Examples of developing country regulation of IVDs**

<table>
<thead>
<tr>
<th>Country</th>
<th>Regulatory body</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>Agência Nacional de Vigilância Sanitária</td>
<td>Mandatory registration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cost of registration depends on the size of the company doing the registration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Products must be reregistered every 5 years</td>
</tr>
<tr>
<td>China</td>
<td>State Food and Drug Administration</td>
<td>No specific regulations aimed at IVD; reagents and instruments require separate registration</td>
</tr>
<tr>
<td></td>
<td>China Quality Certification Centre</td>
<td>Class II devices require testing (disease-specific regulations); class III clinical test data required</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Safety of imported goods checked</td>
</tr>
<tr>
<td>India</td>
<td>Central Drugs Standard Control Organization</td>
<td>Licensing for importation or local manufacture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Public sector requires testing in national laboratory; no controls on private-sector purchasing</td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>Korean Food and Drug Administration</td>
<td>Imported devices require registration; pre-market approval for class II, III and IV devices requires test data</td>
</tr>
<tr>
<td>Nigeria</td>
<td>National Agency for Food and Drug Administration and Control</td>
<td>No regulations aimed at IVDs</td>
</tr>
<tr>
<td>Singapore</td>
<td>Center for Medical Device Registration</td>
<td>New regulations being implemented will require registration of all medical devices by 2011</td>
</tr>
<tr>
<td></td>
<td>Health Sciences Authority</td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td>Plans to establish new agency</td>
<td>NHLS reviews published data or follows international recommendations</td>
</tr>
<tr>
<td></td>
<td>South African Regulatory Authority for Health Products to replace Medicines Control Council</td>
<td>Currently no restrictions on import and use of IVDs (used outside NHLS)</td>
</tr>
</tbody>
</table>
3.5.3 Effect of lack of regulation on quality of diagnostic tests

The absence of regulatory control or a lack of enforcement has resulted in the sale and use of IVDs of variable quality in developing countries. This situation is made worse by a lack of capacity for quality control or quality assurance measures within the laboratory services and regulatory bodies of many countries. Independent performance data are rarely available, and test purchasers are often reliant on data supplied by the manufacturer of distributor. Sale of fake tests is an additional problem, and in countries such as China and India it is difficult for small clinics to know whether the products they are buying are real or substandard copies. Problems also occur with non-commercial in-house and locally produced tests. Poor performance may be due to inadequate test design, substandard manufacturing practices or the application of tests to unsuitable populations. Examples of recently reported problems are heat instability of point-of-care tests for malaria (TDR, 2010), inappropriate test targets due to variation in the strain of virus (Aghokeng et al., 2009) and interference from indigenous infections (Everett et al., 2010). Reports highlighting the variability of test performance of rapid tests for TB, dengue and malaria are available from the Special Programme for Research and Training in Tropical Diseases (TDR, 2008, 2009, 2010).

3.6 WHO prequalification

In the absence of stringent regulatory authorities in most of the developing world, WHO initiated a system for prequalification of medicines and vaccines and then, in 2008, diagnostics. The WHO Prequalification of Diagnostics Programme aims to promote and facilitate equitable access to safe, appropriate, high-quality, affordable diagnostics for high-burden diseases, suitable for use in resource-limited settings. The programme originally gave priority to HIV and acquired immunodeficiency syndrome (AIDS) and malaria but now also includes diagnostics for hepatitis B and C. Western regulatory approval of new diagnostics for use in developing countries may be considered a possible alternative but is not usually tailored to evaluate suitability and adaptability of diagnostics for diseases prevalent in developing countries.

Prequalification, where tests are evaluated against a defined list of quality and performance criteria, could provide a very useful solution. It could create a common ground for ensuring quality of a product on a far more global basis than the current fragmented regulatory systems allow. It would ensure quality of the device, but it does not guarantee batch consistency, for which local quality control would be needed.

Diagnostic companies often produce multiple products for different diseases, based on similar technology platforms, and many companies have access to the same reagents and technologies. Proliferation of diagnostic products requiring regulatory approval presents an enormous challenge to the WHO prequalification programme. For example, in response to a change from syndromic management of fever to evidence-based treatment requiring the use of diagnostics, over 120 malaria rapid tests have become commercially available in the past few years.
Many products that have only just been approved are already outdated – but because they are now listed as approved, they are still being purchased worldwide.

In the absence of international standards, WHO has adopted a process of approval for new tests for TB, whereby evidence on a test’s performance is collated and reviewed by an invited expert committee. The conclusions and recommendations of the committee are considered by the Strategic and Technical Advisory Group for Tuberculosis, which may choose to issue a recommendation with guidelines regarding appropriate implementation of the technology. It should be noted, however, that the high cost of field trials and multicentre evaluation studies serves as a deterrent, and there is a bias towards tests from large companies and those developed in partnership with well-funded organizations.

### 3.7 Summary of the diagnostics landscape

- The field of diagnostics differs from other pharmaceutical sectors. The market value is lower than that for drugs and vaccine, products have a shorter lifespan and there are differences in the regulatory approval process.
- The diagnostics market is expanding, including emerging economies in the developing world, and yet many people in developing countries have poor or no access to the diagnostic tests that are widely available in developed countries.
- Providers of diagnostic services in developing countries include the public and private sectors, non-profit-making organizations and NGOs. Governments are major purchases of diagnostic tests in countries where they are the main providers of primary health care, such as Brazil and South Africa.
- The disease burden is high and improved access to diagnostic tests is badly needed to enable evidence-based treatment, to improve patient outcomes and to reduce problems of drug resistance.
- The regulatory environment for IVDs in the developing world is not conducive to product development: Approval processes are lengthy and not harmonized, and there is a lack transparency. The failure of most developing countries to monitor test quality or effectiveness allows poor-quality and inappropriate tests to be marketed and used, wasting precious resources.
- The implementation of diagnostics in developing countries is impeded by problems of access, affordability, lack of quality assurance and weak health systems that frequently result in stockouts of diagnostics and drugs.
4. Opportunities and absorptive capacity for R&D and manufacturing of IVDs in the developing world

To develop, manufacture and market a diagnostic test is a considerable undertaking that can take 2–10 years at a cost of US$ 10–100 million (Kettler et al., 2004). The pathway by which a new diagnostic device is developed, validated and adopted for public sector use is illustrated in Figure 11.

Figure 11 Bench-to-bedside pathway for diagnostic test research

Production of IVDs for the developing world follows the same pathways as other products, and adequate financing is a key requisite (Figure 12).
4.1 Manufacturing in developing countries

Sustainable local manufacture of IVDs requires that adequate skills and infrastructure are maintained at all stages of the process, including R&D, manufacturing, quality assessment, packaging, marketing and distribution. For novel products it may be necessary to develop new manufacturing processes, and specialist knowledge may be required to engineer and maintain the appropriate facilities.

Manufacturing capacity varies widely across the world. In general, countries in Africa have a much less developed manufacturing base than countries in Asia and Latin America. The low level of technology development is reflected by low levels of investment in capital equipment. During 2002 the region of sub-Saharan Africa (excluding South Africa) imported equipment to the value of US$ 5264 million, whereas investment of east Asia and Latin America in capital equipment was US$ 444 980 million and US$ 1 033 883 million, respectively (Lal & Pietrobelli, 2005). Imports into Kenya and Ghana were 100-fold lower than those of the Republic of Korea and Malaysia. Investment in people may also be taken as an indicator of a country’s capacity; in this respect Africa also lags behind other regions of the world. During 1995–1997 in sub-Saharan Africa (including South Africa), 0.04% of the population were students of technical disciplines (natural sciences, mathematics, computing and engineering). This compared with 1.65% in the Republic of Korea and 0.13% in Malaysia. During

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2 Excluding transport equipment, but including parts and components.
the same period over 1 million technical students enrolled in India, compared
with just 220 660 in the whole of sub-Saharan Africa (Lal & Pietrobelli, 2005).

**Figure 13 Sector expertise required in IVD production**

Figure 13 illustrates the three components of successful test production. The
technical capacity and infrastructure needed to develop and manufacture
da diagnostic test varies with the type of product and the complexity of the
technology (Table 8). Some can be assembled with little need for dedicated
facilities, while others require the manufacture of specialist reagents or
construction of highly sophisticated instrumentation and software. Whereas
microbiological staining solutions are frequently prepared in the laboratories
where they are to be used, tests involving specialist reagents and engineered
platforms are more often manufactured by the commercial sector.

**Table 8 Examples of diagnostic test requirements**

<table>
<thead>
<tr>
<th>Product</th>
<th>Technology requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiological staining kit</td>
<td>Chemical reagents, glass slides</td>
</tr>
<tr>
<td>Immunochromatographic lateral flow device</td>
<td>Purified antigens, specific antibodies, labelling technology, engineered detection platform</td>
</tr>
<tr>
<td>Polymerase chain reaction (PCR)</td>
<td>Sample extraction reagents, reaction mix (e.g. DNA primers, enzymes), thermocycler instrumentation, detection technology</td>
</tr>
<tr>
<td>Automated microbiological culture</td>
<td>Culture media, growth-detection chemistry, sophisticated instrumentation, specialist software</td>
</tr>
</tbody>
</table>

4.1.1 **Good manufacturing processes**

Ensuring that facilities are using GMP would require:

- a skilled workforce provided with regular training, guidelines and standard
  operating procedures;
- audit of facilities by local regulatory/notified bodies to ensure compliance.
4.1.2 Local quality control

Countries importing IVDs need an effective quality assurance system to ensure product consistency and to identify fake products. Such a system has been implemented in some settings whereby every batch undergoes quality assurance validation/evaluation using control panels of test samples supplied by the manufacturer, and a quality certificate is issued. An example of this is NewScen, which sells its HIV tests in South Africa – every batch is checked.

Some laboratories have adopted international standards of quality management to become “accredited” laboratories. The international standard ISO 15189 was developed for medical laboratories by ISO. This provides a means of testing/monitoring competency of testing and calibration in a laboratory. It encompasses sample collection, interpretation of test results, turnaround times, risk management and the education and training of staff. Particularly challenging for developing countries are the components that rely on external factors such as the maintenance of equipment (preventive and curative) and procurement procedures. The system is mandatory in most developed countries but is expensive and time-consuming to implement. The Kenyan Medical Research Institute laboratory in Kisuma estimated the process took 2 years, with pre- and post-accreditation costs of US$ 126 553 and US$ 71 143, respectively (not including equipment and infrastructure maintenance costs) (Zeh et al., 2010). There are currently several initiatives to improve the quality of laboratory services in developing countries and incorporate components of the accreditation process (Nkengasong et al., 2009); however, they focus mainly on the government sector, and private laboratories remain largely unregulated.

Manufacture of IVDs in developing countries is undertaken by commercial and noncommercial organizations. Commercial manufacture may be undertaken by local small and medium-sized enterprises or by subsidiaries of multinational companies. Public–private partnerships have also emerged, where non-profit-making organizations work with commercial partners. Most IVDs manufactured in developing countries are instrument-free devices or are reagents for use with instruments built elsewhere. They frequently target developing country priority diseases such as HIV and malaria. In China it is estimated that local producers have a 60% share of the market, with the remaining 40% of imports being mainly sophisticated tests and instrumentation.

Tests manufactured in less developed countries are usually used in the countries where they are produced. Some non-profit-making producers are not permitted to engage in commercial activity and supply only the public sector. Chinese-manufactured tests are exported to other countries, as are those from India. Tests are exported either directly by the manufacturers or through networks provided by multinational companies.

An example of IVD tests that are used widely in developing countries are rapid tests to detect malaria antigen. In a list of commercial tests published on a WHO website in 2009, two-thirds of companies listed as suppliers were from Europe, North America and Australia, with the remainder being from less
developed countries and emerging economies\(^3\) (the site of manufacture was not provided) (Table 9).

**Table 9 Commercial producers of tests for malaria antigen**

<table>
<thead>
<tr>
<th>Country/region</th>
<th>Number of companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>10</td>
</tr>
<tr>
<td>United States</td>
<td>9</td>
</tr>
<tr>
<td>India</td>
<td>5</td>
</tr>
<tr>
<td>Australia</td>
<td>2</td>
</tr>
<tr>
<td>South Africa</td>
<td>2</td>
</tr>
<tr>
<td>China</td>
<td>2</td>
</tr>
<tr>
<td>Canada</td>
<td>2</td>
</tr>
<tr>
<td>Kenya</td>
<td>1</td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>1</td>
</tr>
<tr>
<td>Indonesia</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>35</strong></td>
</tr>
</tbody>
</table>

### 4.2 R&D in developing countries

Development of diagnostic tests requires identification and validation of markers that are predictive of the disease coupled with a robust system for their detection. Whereas biomarker discovery requires research in biological processes, detection may involve the physical sciences, electrical engineering and instrument design. Although crucial for disease control, diagnostics research for infectious diseases has received relatively little funding compared with other areas of translational research such as drug and vaccine development.

An example is provided in Figure 14, which shows that over the 5 years 2005–2009 diagnostics research received less than 8% of the total funds allocated to TB research.

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\(^3\) See [http://www.wpro.who.int/NR/rdonlyres/3AB34928-4E2D-42FF-9904-58EDD38A7921/0/ProductssubmittedforRnd1_Rev_24MAR09.pdf](http://www.wpro.who.int/NR/rdonlyres/3AB34928-4E2D-42FF-9904-58EDD38A7921/0/ProductssubmittedforRnd1_Rev_24MAR09.pdf).
This lack of attention to diagnostics for infectious diseases is due to a variety of reasons, including:

- lack of value associated with diagnostics in health-care delivery;
- lack of clear product specifications of diagnostics;
- lack of funding initiatives by global donors;
- unclear market demand and forecasting, which prevents companies from undertaking risk of development;
- unclear regulatory pathways;
- unclear procurement and distribution mechanisms.

Against this background it is perhaps not surprising that diagnostics R&D has not flourished in developing countries. Few developing countries have the capacity for translational research, and new product development is confined largely to countries with academic centres of excellence or where investment by the commercial sector has been forthcoming. Examples of R&D on diagnostics that have not progressed to product development are a test for schistosomiasis in Ghana and a test for drug-resistant TB in Uganda (Al-Bader et al., 2010).

The capacity to translate scientific research to protected intellectual property varies across countries. In some countries there has been a strong correlation between the number of scientific publications and the number of patents. In others, such as Brazil, the increase in academic output was not matched by increased patents (Figure 15).
**Figure 15** Comparison of numbers of scientific publications and patents from Taiwan, China, the Republic of Korea and Brazil, 1976–1998

Source: ISI and USPTO (Rapini, 2000)
4.3 Opportunities and absorptive capacity for diagnostics R&D and manufacturing

There are opportunities for cooperation with international partners. This may take the form of partnerships with academic institutions (Box 2), commercial bodies, and non-profit-making organisations such as PATH and FIND. Product development is promoted through sharing of resources. The risks are also shared, and as illustrated in Figure 16. Projects lead to shared rewards, a partnership model for R&D for novel antibiotics first proposed by So et al (2011). The combination of partners is shown in Figure 17. There is a trend towards the formation of public–private partnerships for the development of diagnostic tests for diseases that are endemic in developing countries.

**Figure 16 Accelerating innovation to production: The 3Rs of partnership for diagnostics R&D**

**Box 2 R&D collaboration with academic institutions**

There are numerous examples of collaborations with academic institutions in industrialized countries (Nwaka et al., 2010). They range from biomarker discovery and product development projects to evaluation studies. They may incorporate capacity building through postgraduate training schemes. Three institutions with long histories in the field are the Institute of Tropical Medicine in Antwerp (Instituut Voor Tropische Geneeskunde; ITG), the Royal Tropical Institute, Amsterdam (Koninklijk Instituut voor de Tropen; KIT) and the London School of Hygiene and Tropical Medicine. Success stories include pioneering of light-emitted diode (LED) microscopy by KIT, a technology now widely adopted (Anthony et al., 2006), and an improved test kit for sleeping sickness developed by ITG in collaboration with the producers of the test, the Congolese Institut National de Recherche Biomédicale (INRB) (Buscher et al., 2009).

Recent grant awarding schemes for R&D activities in developing countries have been posted by the Wellcome Trust, the Bill & Melinda Gates Foundation, Canadian Grand Challenges, the European Commission and the United States...
National Institutes of Health. These calls are open only to investigators from developing countries, but they encourage collaboration with developed country partners whose expertise may complement that in developing countries.

**Figure 17 Drivers of R&D for IVDs for diseases of poverty: The trend is towards public–private partnerships**

Two networks have recently been established to promote and support R&D in developing countries, including development of diagnostic tools: the African Network for Drugs and Diagnostics Innovation (ANDI)\(^4\) and the Asian Network for Drugs and Diagnostics Innovation (NDI).\(^5\)

India has established a similar network, and the other countries in Asia are also forming a network under the auspices of the Science and Technology Task Force for ASEAN. In 2012, there will be opportunities to merge these country networks into the Asian Network for Drugs and Diagnostics Innovation. A

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4. “ANDI’s primary objective is to promote and support health product R&D led by African institutions for diseases of high prevalence in the continent. The expected outcome is the discovery, development and delivery of affordable new health tools including those based on traditional medicine, as well as the development of capacity and establishment of centres of research excellence” (http://www.andi-africa.org/).

5. “The Chinese Network for Drugs and Diagnostics Innovation, China NDI, is built with the support of UNICEF/UNDP/World Bank/WHO Special Planning Agency for Tropical Disease Research and Training. The secretariat is based in National Institute of Parasitic Disease, China CDC. Through capacity building, infrastructure development and promotion of cooperation and exchange, China NDI aims to support and aid Chinese researchers and scientists for tropical disease in initiating and developing drugs, vaccines and diagnostic reagents, in establishing a strong cooperation mechanism of non-profit, result-oriented, and government–private partnership including international partners, and in creating new tools and products of independent intellectual property rights to gradually build sustainable win–win R&D model through resources integration and information sharing” (http://www.ipd.org.cn).
similar network for drugs and diagnostics innovation is being planned for South and Central America.

For the first time in many countries, through these networks, science and technology and engineering groups in academia and industry are coming into contact with departments of health and their needs. Such networks, usually aimed at non-health sectors such as communications, household appliances and defence systems, may bridge the vast gap between the need for better diagnostic tests and technology innovation. Providing a forum to interact is only a first step; obtaining funding, finding a common working language and identifying a critical path for the translation of innovative ideas into a diagnostic product are vital elements to be addressed if diagnostics R&D in the developing world are to make a difference.

4.3.1 Biotechnology in developing countries

Biotechnology is flourishing in some developing countries. Among developing countries, the Republic of Korea leads in the number of health biotechnology papers published, followed by China, India, Brazil, South Africa, Cuba and Egypt (Figure 18). There was a tremendous increase in number of publications in 2002 compared with 1991. The vibrancy of the biotechnology sector in developing countries is also in evidence from the number of health biotechnology patents issued by the United States in 2003, where India leads with more than 30 patents compared with 29 from the Republic of Korea, 12 from China and 6 from Brazil.

Many of these researchers are collaborating with biotechnology firms in the developed world. Although there are still many hurdles, such as funding, regulatory issues, “brain drain” and fragmented health infrastructure, the absorptive capacity for diagnostics R&D is promising.

Figure 18 Increase in scientific publications and patents issues

5. Technology transfer to developing countries

Local manufacture may provide commercial and logistical advantages. However, the major benefits are that it offers tailored production of IVDs to suit local needs while reducing reliance on imported goods.

Prospects for improving access to diagnostics for the most vulnerable populations are enhanced by three key factors:

- increased political will arising from recognition that improved access to diagnostics in developing countries will accelerate progress to the Millennium Development Goal;
- recognition of emerging markets by the commercial sector;
- emergence of new point-of-care technologies appropriate for use in developing countries that do not require laboratory infrastructure or highly trained technical personnel.

When stakeholders were asked about local production of IVDs, they identified increased political will, closeness to the market and access to local knowledge as opportunities. Perceived advantages of in situ manufacture over importation included decreased regulatory barriers, reduced foreign currency expenditure, and reduced distribution and shipping costs. It should be noted that although most feel that the lack of regulation is damaging to the industry, some companies see the opportunity to market their tests unhindered by regulatory processes as an advantage.

*Figure 19 Diagram of technology transfer pathway*
There are several models exemplifying transfer of technology for production of IVDs to developing countries. They may involve transfer of technology relating to one or more elements of the IVD production pipeline (Figure 19):

- **R&D**: Transfer of knowledge to develop, optimize and evaluate a prototype test.
- **Manufacturing**: Transfer of knowledge and know-how relating to manufacture and packaging; may include design and tooling of manufacturing plant and the implementation of quality standards.
- **Marketing**: Support for marketing and distribution.
- **No technology transfer**: No external assistance required. Necessary know-how is indigenous or is attained from literature in the public domain.

Participants in technology transfer activities include multinational corporations, small local companies, academic partners and non-profit-making organizations (Figure 20). By far the most frequent instances of technology transfer are from diagnostic companies in the developed world to diagnostic companies in the developing world for the purpose of manufacturing (indicated by a red arrow in Figure 20). Often there is no transfer of technology know-how or any further R&D conducted by the developed country partner. The developed country partners are often located in a country with a large domestic market. Products made under this model are cheaper and can be approved more easily in the recipient country. Technology transfers that are R&D based can involve both the public and private sectors, but because there are few R&D-based companies in the developing world, there have not been many successes. Product development partnerships in the developed world tend to seek out diagnostic manufacturers in the developed world for technology transfer and then negotiate for two-tier pricing for their products. Much of the innovation in recent years for point-of-care and rapid detection technology have come from small and medium-sized companies in the developed world. These companies tend to seek out academia, R&D-based companies or public research institutions in the developing world for partnership, either for further R&D to utilize their technology for diseases of public health importance in the developing world or for manufacturing. This is the ideal model of technology transfer and local production.
Figure 20 Models of technology transfer and local production

Table 10 offers some examples or technology transfer. It should be noted that not all technology transferred leads to successful products; for example, the transfer of simple immunochromatographic technology for detecting antibodies and antigens has been successful for some diseases such as malaria, but poor-quality tests for other diseases have also been produced, some of which continue to be sold.

Table 10 Examples of technology transfer

<table>
<thead>
<tr>
<th>Technology transfer</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfer of manufacturing by multinational company. In this model manufacturing technology is transferred to a subsidiary site in a developing country</td>
<td>A United States based company, Orasure Technologies Inc., has contracted a company in Thailand to assemble its OraQuick HIV device</td>
</tr>
<tr>
<td>Diagnostic R&amp;D by multinational company at the developing country site. In this model product development but not manufacture is undertaken at the subsidiary site</td>
<td>Development of molecular test for mycobacteria in South African laboratories by Roche Diagnostics. The test was designed to meet the needs of South Africa, which has a significant number of cases of pulmonary infection with mycobacteria other than TB</td>
</tr>
</tbody>
</table>

Continues…
5.2 Technology transfer and productive capacity for diagnostics.

This section contains examples of recipients of technology transfer for local manufacturers of IVD.

5.2.1 Fiocruz

The Oswaldo Cruz Foundation (Fiocruz) is one of the world’s most successful recipients of technology for diagnosing infectious diseases. Fiocruz is a Brazilian scientific institution for R&D affiliated to the Brazilian Ministry of Health that has developed and produced IVDs both independently, and in collaboration with international commercial partners. In 1976 it established the Immunobiological Technology Institute (Bio-Manguinhos), a technological unit that produces vaccines and diagnostics, focusing on diseases of national priority. It produces reagents for diagnosis of infectious and parasitic diseases, including HIV, leishmaniasis, Chagas disease, dengue fever, hepatitis and rubella. During 2008 Fiocruz produced over 5 million diagnostic reagents. Bio-Manguinhos observes GMP and its products have the stamp of the National Health Surveillance Agency (ANVISA). Fiocruz has signed a series of technology transference agreements with Chembio Diagnostics, a United States-based company specializing in rapid diagnostic tests. The agreements give Fiocruz access to a second-generation lateral flow test platform, the Dual Path Platform (DPP), a rapid immunoblot for serologic HIV infection confirmation and reagents that are proprietary to Chembio. The technology transference process included access to technical documentation, personnel
training and exchange visits. The agreement incorporated a minimum quota of purchases by Fiocruz from Chembio, on the understanding that once the technology transfer process is complete royalties would be paid. In 2010 the company reported approval of its DPP HIV 1/2 screening and confirmatory tests by ANVISA. Regulatory approvals for the DPP leptospirosis and syphilis-treponemal tests are pending, and submission of the multiplex Syphilis Screen & Confirm test is anticipated during 2011. In 2011 Bio-Manguinhos received regulatory approval from Brazil’s Ministry of Agriculture, Livestock and Food Supply to market Chembio’s DPP visceral canine leishmaniasis test. As a result of this initial regulatory approval, Chembio anticipates submitting the product for CE marking and potentially United States FDA approval, so that the product can be further commercialized in other affected regions. Chembio also has under development a new DPP test for Chagas disease, which is endemic to Brazil.

Fiocruz has benefited from access to a large market through using the purchasing power of the Ministry of Health. Brazil has a population approaching 190 million, of which an estimated 150 million people are users of the National Health System. Within the public sector 400 million diagnostic tests are authorized annually.

5.2.2 Republic of South Africa

South Africa is presented as one of the few countries in Africa with a high burden of infectious disease that has a nascent programme of technology transfer for local production of diagnostics. It exemplifies a country of high need but where opportunities for local manufacture have yet to be fully exploited. It has a population of approximately 50 million, 90% of whom live in or around 5 major urban centres. With a large population at risk of infection and a government committed to improving the health of the population, South Africa has considerable market potential. It also has the strongest economy in southern Africa and is a net exporter to countries of the region. Projected gross domestic product (GDP) (purchasing power parity, PPP) for 2010 is US$ 521.878 billion and GDP (PPP) per capita is US$ 10 466 (IMF, 2010). South Africa has an established manufacturing base and good infrastructure, but current manufacturing of IVDs is limited in scope and extent. There is potential for commercial exploitation, but opportunities to obtain investment are limited (Masum & Singer, 2010). The Technology Innovation Agency is funded by the Department of Science and Technology to support and enable technological innovation to achieve socioeconomic benefits for South Africa; however, its health sector portfolio has so far not included IVDs.

Current national health priorities are HIV/AIDS, TB, screening for cervical cancer and misuse of alcohol. The HIV prevalence rate is approximately 10.6%. (17% for people aged 15–49 years), with about 5.21 million people living with HIV/AIDS (Statistics South Africa, 2009), and HIV/AIDS is the leading cause of death (28.8%). The estimated TB incidence during 2009 was 490 000 (970 per 100 000 population) (WHO, 2010a). It is estimated that 76% of incident TB cases are detected and notified. The emergence of drug-resistant forms of TB
and HIV has worsened the situation. Other infections of note include sexually transmitted infections, upper respiratory tract infections and, in some regions, malaria. A measles epidemic commenced in late 2009, with over 10 000 cases notified in the first 6 months of 2010 (National Institute for Communicable Diseases, 2010a).

South Africa has a mixed system of health care, incorporating public, private and traditional healers. Public-sector care is free at the primary level. Both the public and private sectors have expanded in recent years. The mining industry also provides health care for its employees. Estimated health-care spending per capita (PPP) is US$ 869, and estimated Government health-care spending per capita is US$ 364 (WHO, 2010b). The private sector provides tertiary care to patients from countries in the region where high-quality care is not available. The major provider of diagnostic services at the primary health-care level is NHLS, a non-profit-making organization established by an Act of Parliament. There are also commercial laboratories providing to the private sector. NHLS encompasses a national network of 265 pathology laboratories throughout the country. The services offered include consultation on specimen collection and management, testing and disposal, and interpretation of results. NHLS provides laboratory diagnostic services (e.g. surveillance studies) to the Department of Health, provincial and district hospitals, primary health-care clinics and other state institutions (e.g. prisons). It also offers a referral diagnostic service to private-sector health-care providers for less frequently requested tests and expensive tests. During 2009 NHLS performed 2.95 million CD4 count tests, 1.2 million HIV viral load tests and 244 685 diagnostic HIV-1 PCR tests (National Institute for Communicable Diseases, 2010b). Over 3 million diagnostic microscopy tests for TB were performed and a further 800 000 TB cultures using a commercial test kit (Erasmus et al., 2010). New molecular technology to test for TB drug resistance was recently introduced at considerable economic cost.

**Regulatory control**

The South African National Accreditation System gives formal recognition that laboratories, certification bodies, inspection bodies, proficiency testing scheme providers and GLP test facilities are competent to carry out specific tasks. It is responsible for the accreditation of certification bodies to ISO/IEC 17021, ISO/IEC 17024 and 65 (and the IAF interpretation thereof), and laboratories (testing and calibration) to ISO/IEC 17025. Inspection bodies are accredited to ISO/IEC 17020 standards. GLP facilities are inspected for compliance to Organisation for Economic Co-operation and Development (OECD) GLP principles. However, there are no specific regulatory requirements regarding diagnostic tests. Within NHLS, procurement decisions are often made centrally, sometimes with in-house validation before awarding of tenders. There are no such limitations for private laboratories. It is a competitive market, with some tests having FDA approval or CE marking. A new South African Regulatory Authority for Health Products has been proposed to replace the Medicines Control Council.
The IVD market

The South African IVD market has expanded over the past 7 years. Revenue for 2009 was estimated at US$ 64 million. This is forecast to rise to US$ 98 million by 2016, at an estimated compound annual growth rate (CAGR) of 6.3% (GBI Research, 2010). However, economy measures within NHLS to reduce the numbers of tests performed may reduce growth. The largest sector of the commercial market is clinical chemistry,\(^6\) followed by immunochemistry.\(^7\) The fastest-growing areas are infectious immunology\(^8\) (8% CAGR) and genetic testing (8.2% CAGR). Over 20 IVD marketing companies operate in South Africa. The market is dominated by products from large multinationals with manufacturing capacity based in industrialized nations (Table 11) (GBI Research, 2010; Competition tribunal of South Africa, 2006).

**Table 11 Share of South African IVD commercial market by value**

<table>
<thead>
<tr>
<th>Company</th>
<th>Estimated market share (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbot</td>
<td>39</td>
</tr>
<tr>
<td>Roche</td>
<td>26</td>
</tr>
<tr>
<td>Beckman Coulter</td>
<td>9</td>
</tr>
<tr>
<td>Bayer Diagnostics</td>
<td>9</td>
</tr>
<tr>
<td>Siemens/DPC</td>
<td>7</td>
</tr>
<tr>
<td>Dade Behring</td>
<td>2</td>
</tr>
<tr>
<td>Ortho Clinical Diagnostics</td>
<td>2</td>
</tr>
<tr>
<td>Others</td>
<td>6</td>
</tr>
</tbody>
</table>

There has been consolidation of IVD companies, with a number of mergers and acquisitions. Alere Inc. (formally Inverness Medical Innovations) acquired two South African IVD manufacturing companies in 2008, one of which appears to have ceased trading.

A number of in-house assays are used in the larger hospitals and research institutions. These are mainly molecular tests (PCR) developed for specific pathogens or conditions.

**In-country IVD manufacturing capacity**

Local IVD manufacturing capacity is restricted to simple diagnostic technologies for malaria, HIV, schistosomiasis, HCG, hepatitis B surface antigen (HBsAg), syphilis, CD4 S/P, bilharzias, and some pregnancy tests and urine dipsticks.

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\(^6\) Tests, reagents and instruments for measuring enzymes, metabolites, electrolytes, sugars, lipids, proteins and small molecules in body fluids (not including immunoreagents).

\(^7\) Tests, reagents and instruments for analysing proteins, hormones, drug moieties and non-infectious diseases.

\(^8\) Tests and reagents using antibody–antigen reactions to diagnosis bacterial or viral infections.
Two companies manufacture on a large scale and export to the global market. Vision Biotech, previously an independent privately owned company, was acquired by Inverness Medical Innovations in 2008 and rebranded as Alere Healthcare Pty in 2010. ICT Diagnostics also sells rapid tests for infectious diseases to the international market.

**R&D capacity**

South Africa has a thriving medical research community attracting national and international funding, particularly for HIV and TB. Activities include the evaluation of new diagnostics tests. However, translational research in the area of diagnostic test development has been very limited.

The educational sector includes 22 universities, including 6 technology colleges and 8 medical schools.

NHLS incorporates the former South African Institute for Medical Research, the National Institute for Virology and the National Centre for Occupational Health and undertakes research in collaboration with the university sector.

R&D is also undertaken by local companies such as Vision Biotech and as partners in multinational companies. Examples of this include Roche Products (Pty) Ltd, which contributed to a new test for TB and other mycobacteria found in the South African population, and QuantuMDx, an international company seeking to develop novel point-of-care molecular platforms (the South African branch of this company closed during 2010).

### 5.2.3 Kenyan Medical Research Institute

In this example we present a product development initiative at the Kenyan Medical Research Institute (KEMRI). In this initiative, investment by the Kenyan Government and an international donor succeeded in establishing manufacturing capacity, but reliance on a small local market and a single technology proved to be an unsustainable business model. In addition to other sources, information has been distilled from a case study funded by the Bill & Melinda Gates Foundation and published in a supplement of *BMC International Health and Human Rights* (Simiyu et al., 2010).

KEMRI was established in 1979, growing out of the East African Medical Institute that had been established 6 years earlier. It is part funded by the Kenyan Government and has also received funding from a number of international collaborating partners, including the Japanese International Cooperation Agency (JICA). Research on diagnostic kits began during 1998 with the assistance of JICA, and a test for hepatitis B was developed to screen blood collected for transfusion (Okoth et al., 1999). The test was initially produced on a small scale for local use, but in 2005 work started on construction of a manufacturing facility that would permit production on a commercial scale. The plant was co-funded by JICA and the Government of Kenya and opened in 2007 to produce two kits based on particle agglutination technology (hepatitis
B and HIV). Following a change in the WHO recommendation on testing blood products, agglutination tests were dropped in favour of enzyme-linked immunosorbent assay (ELISA)-based technologies. The Kenyan Government duly stopped purchasing the KEMRI test, leaving KEMRI without a market for its product. Attempts have been made to diversify into other products, including rapid immunochromatographic tests and a disinfectant. However, KEMRI was dealt another blow with the levelling of corruption charges against its former director and other senior figures by the Kenyan Anti-Corruption Commission. KEMRI is a founder member of ANDI and, although not currently used, it is hoped that the manufacturing facility and the lessons learnt may provide foundation for future initiatives.

6. Challenges

There are considerable obstacles to be overcome if access to diagnostics in developing countries is to be improved. Unfortunately the barriers to successful and sustained local IVD production are high, and there are many examples of failed initiatives. Examples of problems reported by test developers include the following:

- blocked by lack of access to intellectual property – e.g. access to intellectual property blocked when company underwent acquisition;
- market flooded by cheap and low-quality imports;
- external R&D funding withdrawn from test developers because of quality issues;
- test discontinued following acquisition of company;
- rationalization of product lines following acquisition (changed site of manufacture);
- unable to attain sufficient finance;
- technology did not meet stringent product specifications;
- inadequate stability of reagents for tropical climate;
- unable to compete with existing procurement arrangements.

There was a consensus among stakeholders consulted during this project that current business models do not address the needs of vulnerable populations and that new business models for diagnostics are essential.

The following views were expressed during consultation with stakeholders:

“There is a poor understanding and acceptance of value of diagnostics. This is often a consequence of inadequate diagnostics.”

“The private sector is not responsive enough to the needs of developing countries. Governments and multinationals should take the initiative to address public health needs in a specific timeframe so as to mobilize effectively resources and capabilities for action. Developed country manufacturers must take the lead and establish partnerships in developing countries. South–south partnerships should be encouraged, as the north is not responding adequately to the needs of developing countries.”
“Traditional business models might work for HIV/AIDS, malaria and TB but will not work for other neglected diseases.”

“Poor market incentive for some diagnostics products means existing models do not work for low- and middle-income country needs.”

“New business models are essential to provide manufacturing capacity through public–private partnerships in order improve access to medical technologies. They should encourage test development in developing countries. There is a need to change the culture of companies in the developed world and to have them work more with companies in the developing world in the area of R&D.”

“There is a substantial need for new business models as the existing ones are insufficient and inadequate. It is often the case that it is cheaper to import tests from abroad than to actually purchase the local ones. In addition, the perception that the latter products are of worse quality is common.”

“The focus should be on market and financial issues as they remain the most important hurdles facing technology transfer for local production. Small innovative companies are eager to take risks even for small awards, but in the dominant business model, it doesn’t work when the risk is higher and the awards lower.”

“Although South Africa has good capability for local production and many ideas are created, there are still few ways forward to develop new products. Unfortunately, there is a tendency of ‘exportation’ of the best scientists of South Africa to the north, where they get better incentives for work. The country lacks a venture capital environment. Human capacity development is very important.”

“Diagnostics is still a small part of the pharmaceutical sector’s overall business. It doesn’t rank sufficiently high on the health agenda of many governments.”

“Local production will not solve all the problems. The importance of diagnostics needs to be further emphasized.”

“Technology transfer should be framed in terms of: (i) manufacturing, (ii) R&D, and (iii) access per se. Governments have a crucial role in decisions and they should reconcile priorities between these three areas. More partnerships need to be established between stakeholders and that this requires a change of culture in the developed world to foster more collaboration with developing countries.”

“Involvement of governments is of crucial importance as they provide the bulk of medical care in developing countries. They thus need to be made more aware about the implications of lack of access to diagnostics on the future public health situation in their countries and economic prospects.”
“There is lack of clarity on roles of industry, government’s ministries, NGOs, WHO and other agencies – in general there remains insufficient collaboration.”

A number of specific deficiencies were identified during this project:

6.1 Financial and market concerns

- **Financial return:** In the commercial sector decisions are based on rational risk–reward calculations. Financial returns are lower in diagnostics than in other sectors of the pharmaceutical manufacturing industry, such as drugs. The market is smaller, and both profit margins and the volume of sales are reduced. Product life is also shorter, as new replacement technologies are adopted. IVD companies have remained smaller in size than the large drug-based pharma companies, and consequently investment in R&D and manufacturing capacity is on a more modest scale. Additional concerns arise from the ability of developing countries to purchase IVDs and the need to suppress pricing to levels affordable by the world’s poor.

- **Commercial interest:** 80% of the global diagnostics market for infectious diseases is in the developed world. Consequently, the successful companies tend to focus on that market, as that is where the highest demand exists. There is not sufficient financial incentive to introduce production in developing countries – hence, the dialogue with external manufacturers can be of limited effectiveness.

- **Investment opportunities:** Poor market incentives dissuade investment from the commercial sector. Venture capital financing is rarely available in developing countries (Masum et al., 2010). Ownership of intellectual property in the form of patents or know-how is usually required to lever investment funds.

- **Market research:** There is a lack of market research, market data and market segment analysis on which to base investment decisions. Better forecasting models are needed to increase efficiency of local production and reduce costs.

- **Government commitment:** There is a lack of commitment of governments in developing countries to R&D and the manufacture of health products.

- **Political will:** The political will to facilitate local production and purchase local products is lacking, and in some countries local goods are presumed to be inferior to imported goods.

- **Freedom to operate:** Non-profit-making manufacturers, such as those attached to government-run institutions, may not be permitted to engage in commercial activity.

- **Access to market:** The local market may be inaccessible due to competing suppliers offering cheaper imports, a wider range of goods or in some cases inducements to secure contracts.

- **Market value:** The local market may not support manufacture on a cost-efficient scale. The market may be distorted by the distribution of devices by international agencies at reduced cost or donated at no cost.

- **Currency fluctuations:** In some countries unstable currencies and fluctuating exchange rates introduce additional financial risk.
Acquisitions and mergers: Where companies merge with or are bought by large multinational companies, local control over product lines may be lost. There have been cases of local production of IVDs for infectious diseases being discontinued due to consolidation by the parent company following acquisition.

6.2 Intellectual property

There is a tension between the need to protect intellectual property and the need to exploit knowledge. Protection of intellectual property or know-how is seen as vital by test developers who rely on external investment from the commercial sector. Similarly, some noncommercial investors and funding bodies within academia expect and encourage patent protection. However, restricted freedom to operate (denied access to patented technology) can disrupt development or delay implementation.

Intellectual property for IVDs may apply to the exploitation of biomarkers and the technology platform used to detect them. Licensing of technological know-how may be required.

Small companies or institutions that have developed new tests or platforms may not have the funds to take out and maintain patents, and they may not be willing to collaborate with other organizations (especially larger companies) because of a fear of being exploited and losing their intellectual property to another company. There is a lack of knowledge and finance to obtain intellectual property protection and therefore a lack of shared information among test developers.

There is difficulty in finding the appropriate people in large multinational companies to speak to, which discourages collaboration.

Intellectual property may influence access to diagnostics in developing countries, as the price barrier is often associated with intellectual property.

The relatively small revenue from diagnostics and the high expense of maintaining a patent means that intellectual property protection may be sought in a restricted number of countries rather than globally.

There is a lack of a clear inventory of existing devices and related intellectual property.

Patent attorneys may be overzealous in their approach when recommending protection of intellectual property.

Box 3 Case study

The difficulties and delay that may be caused by intellectual property problems were illustrated during transfer of technology by PATH, a non-profit-making organization, to a company in India. PATH has developed a rapid test for gonorrhoea using monoclonal antibodies from a small/medium-sized enterprise based in the United States. When PATH was planning the technology transfer to the Orchid Group of diagnostic companies in Goa, India, the United States company was acquired by a third party, another United States-based commercial company. The resulting intellectual property issues delayed the transfer of the technology for this test for over 3 years.
6.3 R&D

- lack of government commitment;
- lack of financing and capital investment;
- lack of market research, awareness of local needs and target product profiles;
- lack of skilled personnel, reflecting the lack of career opportunities and many research scientists from developing countries seeking employment overseas;
- translational research is not highly esteemed in the international academic community, there is no voice from low- and middle-income countries, and there is a lack of a critical path for success;
- lack of access to well-characterized samples;
- lack of access to equipment and specialist facilities;
- lack of access to reagents;
- lack of access to technology platforms (know-how or patent-protected).

6.4 Manufacturing capacity

- lack of financing;
- lack of GMP capacity and lack of expertise in ISO manufacture, packaging and distribution;
- lack of expertise – skilled local workforce, staff for running, maintenance and repairs;
- lack of infrastructure – power supply, location, transport, regular flooding;
- inadequate and unreliable supply of basic components – pipettes, basic supplies, import duty associated with supplies, biological supplies (antibodies, antigens, importing issues), production supplies (packaging, labelling); peripheral supplies can be very expensive to buy locally, resulting in the final product costing too much to be competitive in the market.

6.5 Approval and regulatory control

- Lack of regulatory control:
  - lack of enforcement permits sale of competing low-cost poor-quality tests;
  - lack of capacity to regulate diagnostic products developed locally;
  - lack of clear guidelines on how to evaluate diagnostics to ensure quality;
  - lack of availability of quality control/challenge panels with which to assess quality and identify fake tests;
  - reliance on approvals by external regulatory authorities (e.g. FDA) – such approvals may not be focused on suitability and adaptability to developing country settings.

- Lack of harmonization:
  - confusion and lack of harmonization make registration in multiple markets costly and slow;
harmonization of existing procedures would allow buyers to choose tests based on a rigorous and universal regulatory system;

- manufacturers have to interact with multiple regulatory agencies and notified bodies at high cost, and many smaller companies do not participate in global discussions on diagnostic regulation and harmonisation efforts;
- terminology and nomenclature need to be harmonized.

- WHO prequalification is seen as a step in the right direction, but it has long timelines and duplication with other agencies and does not include all relevant products.

7. Measures to facilitate technology transfer and local manufacture

In addition to mapping current obstacles to local production, a number of measures to facilitate technology transfer and improve access to diagnostics in developing countries were identified during this project. Prominent among these was the need for advocacy.

To influence public policy and resource allocation and ensure a more favourable climate for diagnostics R&D and manufacture in developing countries, it is necessary to enhance the awareness of national and international bodies to the health, social and economic benefits of improved access to diagnostic tools. It is important that governments understand the impact of a failure to diagnose and control an infectious disease, on communities and on national outputs and economies. Governments must be persuaded that this is not only about disease control but also about the future of their country, including its economy.

It is important that the international community appreciates the needs of the diagnostics industry and recognizes that there are substantial differences between this sector and those dealing with drugs and vaccines.

Advocacy is needed to inform the pharmaceutical industry of the importance of tests for infectious diseases and of the opportunities to work with developing countries.

Most health care in developing counties is provided by the governments, and so it is vital to involve the governments in these discussions. There should be integrated government policies across ministries of health, science and technology, trade and finance to promote local diagnostics industry.

Successful initiatives should be celebrated, and countries with existing political commitment cited as champions or models.
Advocacy is needed for increased investment in R&D, technology transfer and manufacturing capacity by national governments, international donors, and commercial and non-profit-making organizations. Collaboration (north–south and south–south) must be nurtured, including commercial/noncommercial partnerships.

Advocacy is needed regarding regulatory issues that must be addressed at the transnational level, with input from developing countries and test developers.

Stakeholders consulted during the project made a number of suggestions for enhancing technology transfer and manufacturing in developing countries:

- **New business models**: Traditional market-led business models have largely failed to address the health needs of the world’s poorest populations. For manufacturing in developing countries to be sustainable, alternative strategies by which to attract investment are required. These include partnership between the commercial and noncommercial sectors; partnership between small local companies and larger international commercial companies; and social business models/social entrepreneurship programmes. R&D need not always be carried out together. At the moment, both the research and the development are commonly taking place in the developed world. Alternative models might be applied, where in some circumstances it would be beneficial for the initial research to continue in the developed world but to move the development and manufacture to the developing world. Market guarantees, market subsidies, prize funds and market aggregation mechanisms should be explored as a means of lowering barriers for entry to the market.

- **Improved regulatory climate**: Current political will should be exploited to increase regulatory enforcement of diagnostics to increase transparency and encourage commercial entities to participate in local production. Countries can seek collaborations with larger regulatory bodies for guidance. Harmonization must be encouraged, with support for international and regional initiatives. A repository of regulatory standards should be created.

- **Market research**: Thorough market analyses should be undertaken to explain the market demand, pricing, regulatory environment, manufacturing capacity and distribution networks in countries (roadmap to market entry). Such analysis should be made readily available to IVD manufacturers and potential investors.

- **Appropriate technologies**: Normative guidance on appropriate product specifications of diagnostics should be made available to test developers and manufacturers. Each disease and syndrome should have a target product profile.

- **GMP**: Ensuring that facilities are using GMP will require skilled staff who are provided with regular training, guidelines and standard operating procedures and audit of facilities by local bodies to ensure compliance. A training team should be established to build capacity for GLP/ISO manufacture in developing countries. Workforce training programmes should be established (e.g. master’s degree in production/manufacturing or distribution and marketing).
• Quality control: Panels of test samples should be made available to enable purchasers and users of diagnostic tests to monitor quality and detect fake tests. Manufacturers should have a role in making panels available to the customer.

• Communication and collaboration: A forum should be sought to facilitate collaborative problem-solving during R&D instead of competition. An information clearinghouse might be established for dissemination of market analysis, technical briefs, policy briefs and intellectual property relating to diagnostics for developing countries. Consideration should be given to the creation of a global diagnostics association for test developers and manufacturers.

• Intellectual property: Advice and training should be made available regarding intellectual property protection and licensing procedures. Information on patents and the countries where they apply should be collated and made accessible, with regular updates provided. Greater transparency should be encouraged. Open-platform systems, where access to technology is not restricted by intellectual property, would accelerate uptake of technology and its application to multiple diseases. Companies should be encouraged to cooperate on public health products.

• Coordination: the respective roles of international bodies such as WHO, the United Nations Programme on HIV/AIDS (UNAIDS) and the various funding and regulatory bodies should be clarified. Clear leadership and avoidance of duplication is required.

• Guidance: A roadmap should be complied for technology transfer specific to diagnostics, based on previous successful examples.

8. Recommendations

This report makes a number of recommendations. These are focused mainly on the role that international organizations working in partnership with others can take with respect to transfer of technology and local production of diagnostics in developing countries.

Three major approaches need to be taken to promote, support and develop the transfer of technology and local production:

8.1 Promote

To promote technology transfer and local production as a means of improving access to diagnostics:

• Advocacy should be undertaken to:
  – inform the pharmaceutical industry of the importance of diagnostic tests for infectious diseases and of emerging markets in developing countries;
  – ensure the international community appreciates the needs of the diagnostics industry and recognizes that there are substan-
tial differences between this sector and those dealing with drugs and vaccines;
– influence public policy and resource allocation and ensure a more favourable climate for diagnostics R&D and manufacture in developing countries;
– showcase successful initiatives – countries with good models and political commitment for technology transfer and local production should be cited as champions.

• Thorough analysis of the potential market should be undertaken and made available to test developers, potential investors, international donors and local stakeholders.
• Capacity should be enhancing within developing countries to use new diagnostic and manufacturing technology. A clearinghouse should be set up to facilitate communications regarding training and investment possibilities.
• Excellence in diagnostic expertise should be recognized. A professional career path should be established and made accessible to those working in developing countries. Workforce training programmes should be established (e.g. postgraduate degrees in diagnostics R&D, diplomas in production/manufacturing or distribution and marketing).

8.2 Support

To support technology transfer and local production:
• Guidance on required test specifications should be provided. Normative guidance on appropriate product specifications should be made available to test developers and manufacturers, including guidance on pricing.
• A critical pathway for technology transfer to developing countries for the production of diagnostic tests should be determined. Normative guidance on technology transfer activities and how to set up a GMP facility should be published, with examples of best practice.
• The tension between the need to protect intellectual property and the need to exploit knowledge needs to be recognized and addressed:
  – Information on patents and the countries where they apply should be collated and made accessible, with regular updates provided.
  – Advice and training should be made available regarding intellectual property protection and licensing procedures.
• Capacity building for manufacture is required:
  – A training team should be established to build capacity for GLP/ISO manufacture in developing countries.
  – Panels of test samples should be made available to enable purchasers and users of diagnostic tests to monitor quality and detect fake tests.
• Capacity building must be supported to increase the number of stringent regulatory authorities in developing countries.
8.3 Develop

- To develop new models and mechanisms to enhance technology transfer and local production:
  - New business models and approaches to financing and marketing of diagnostics must be created and sustained:
  - The models must include innovative mechanisms for protecting intellectual property, while maximizing access to new technology in developing countries.
  - Alternative financing initiatives must be pursued as a means of lowering barriers for entry to the market, including market guarantees, market subsidies, prize funds and market aggregation mechanism.
  - Incentives for north–south and south–south exchanges and partnerships must be explored.

- Regulatory issues must be addressed at the transnational level, with input from developing countries and test developers:
  - Regional harmonized regulatory standards should be created.
  - Harmonization and transparency must be encouraged, with support for international and regional initiatives.
  - A handbook or “how to” manual to obtain regulatory approval in each country should be developed.

- Consideration should be given to the creation of a global diagnostics association for test developers and manufacturers, similar to IFPMA and with a code of conduct.

- A centre and forum for global diagnostics should be established to coordinate, collate and distribute information and encourage collaboration and harmonization. An information clearinghouse should be set up for dissemination of market analysis, technical briefs, and policy briefs relating to diagnostics for developing countries, and to facilitate identification of potential partners in country.

- A generic model for health technology assessment for diagnostics should be established to allow developing countries to determine whether a new diagnostic technology addresses a country’s public health needs.
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