Tropical Medicine and International Health doi:10.1111/j.1365-3156.2011.02852.x

VOLUME 16 NO 11 PP 1439–1449 NOVEMBER 2011

Quality of medical devices and *in vitro* diagnostics in resource-limited settings

Marcella Mori[1,4], Raffaella Ravinetto[2] and Jan Jacobs[1,3]

1 *Unit of Tropical Laboratory Medicine, Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium*
2 *Clinical Trials Unit, Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium*
3 *Department of Medical Microbiology, Faculty of Health, Medicine and Life Sciences, Maastricht, The Netherlands*
4 *Operational Unit Genito-pathology, Operational Directorate Bacterial Diseases, Veterinary and Agrochemical Research Center, Brussel*

Summary The phenomenon of poor-quality medicines in resource-limited settings is well documented, and field observations reveal similar problems with medical devices (MDs) and *in vitro* diagnostics (IVDs). In scientific literature, however, there are only scarce reports and documents providing evidence of quality problems of MDs or IVDs in resource-limited settings. This discrepancy may be ascribed to (i) the poor regulatory oversight of MDs/IVDs in resource-limited settings, (ii) a general lack of awareness of the problem of poor-quality MDs/IVDs amongst the scientific community and decision-makers, and (iii) poor quality assurance in diagnostic laboratories in resource-poor settings, precluding tracing quality problems of IVDs from the other potential causes of diagnostic inaccuracy. The problem of poor-quality MDs/IVDs in resource-limited settings is a complex one to address. Firstly, operational definitions for substandard and counterfeit MDs/IVDs are required, as well as *ad hoc* field surveys, to ensure proper appraisal of the real extent of the problem. Investments are needed to reinforce the national regulatory oversights on MDs/IVDs in resource-limited settings, and to encourage a proactive and transparent exchange of information between Northern and Southern regulatory authorities. Industrialized countries can play a role by expanding and strengthening their regulatory oversight and quality labels to those MDs/IVDs that are frequently used in resource-poor settings. Hopefully, the combination of these measures will result in better protection of patients in resource-poor countries from the effects of being exposed to poor-quality MDs and IVDs.

keywords medical devices, *in vitro* diagnostics, quality problems, regulatory surveillance, poor countries

Medical devices and *in vitro* diagnostics: poorly regulated in resource-limited settings

Medical devices (MDs) and *in vitro* diagnostics (IVDs) are – simply speaking – medical instruments, apparatus or materials used on patients for surgery, treatment, or diagnosis. Unlike medicines, their intended primary action is not metabolic, immunological, or pharmacological. MDs encompass a wide range of products, from tongue depressors and medical thermometers to complex equipment. IVDs are MDs used for *in vitro* examination of human specimens (European Commission 2011a) and are particularly the subject of this article. Examples include laboratory reagents, rapid diagnostic tests, calibrators and control kits.

The market sales of MDs and IVDs are expected to rise by 50% in 2014 (Visiongain 2008), which reflects their increasing role in healthcare. Therefore, the availability of MDs and IVDs of assured quality is a critical prerequisite to effective and safe healthcare. However, large gaps between the North and South exist, not only in terms of access to MDs and IVDs (Zarocostas 2010) but also in terms of quality assurance. The Global Harmonization Task Force (GHTF) groups countries with stringent regulatory systems for MDs/IVDs, which include Australia, Canada, the European Union (EU), Japan and the United States (US). Unlike them, most resource-limited countries lack the means to ensure appropriate regulatory control (WHO 2010a) and are consequently more exposed to the risk of low quality products.

Notably, definitions of poor-quality products exist in the field of medicine: 'substandards' are genuine medicines produced by legitimate manufacturers that do not meet quality specifications set for them, whilst 'counterfeits' are deliberately and fraudulently mislabelled with respect to identity and/or source (WHO 2010b, 2011a,b). But because no definitions of poor-quality products have been

agreed for MDs/IVDs, it is more difficult to assess their presence and their impact on global health. For operational purposes, and pending harmonized definitions, counterfeit IVDs could be – in line with counterfeit drugs – defined as deliberately mislabelled products (e.g. by expiry date or product identity label), whereas substandard IVDs are those that (i) do not meet the specifications described in the literature (e.g. the case of Giemsa stain with debris) or claimed by the manufacturer (e.g. as listed in the product information sheet) and/or (ii) have apparent errors in labelling or on the product information sheet.

Quality of MD/IVDs in resource-limited settings: observations and literature search

Working with partner organizations in the South, we collected several anecdotal observations of poor-quality IVDs, particularly from Africa (Figure 1). Examples include counterfeits, e.g. diagnostic kits with falsified expiry dates and substandards, e.g. poorly-labelled IVDs or IVDs generating inconsistent results. In addition to field observations, we recorded many shortcomings and non-conformities in a formal survey on the quality of packaging and information inserts of malaria rapid diagnostic tests (Gillet *et al.* 2010). Other groups (Bonnet *et al.* 2009) have reported inadequacy of IVDs developed for a strictly regulated market, when used in field conditions.

To better assess the extent of the problem of low quality MDs/IVDs in resource-poor settings, we performed a literature search. We extracted English and French documents published up to January 1, 2011 from eight databases (WebSPIRS5, Bioline international, African Index Medicus, TechNet21, Popline/the INFO project, the Cochrane Library, PubMed and Google Scholar), by using 21 keywords ('quality and laboratory', 'medical device', '*in vitro* diagnostic', in addition to 'counterfeit', 'fake', 'substandard' – alone or associated with 'medical device', '*in vitro* diagnostic', 'laboratory', 'test', 'kit'). Overall, of 6212 hits, we found 62 documents (1%) on the quality of MDs/IVDs, 31 (0.5%) of those concerning countries not belonging to the GHTF (Table 1). Notably, when using keywords of broader meaning ('counterfeit', 'fake', 'substandard' standing alone, 6192 hits), we also found papers on quality of medicines, which were by far more numerous than those retrieved for MDs/IVDs (478 *vs.* 41, 7.7% *vs.* 0.6%) and were mainly published after the year 2000 (152/164, 92.7%).

Type of quality problems with MDs or IVDs reported in non-GHTF countries

Amongst the 31 documents included in this review (Table 1), there are seven comparative studies from various geographical areas. All show evidence of poor technical performance of some MDs/IVDs compared with the reference method/product (Liu & Lam 2001; Bimenya *et al.* 2003; Subhash *et al.* 2006; Volkow *et al.* 2006; Souza Antunes *et al.* 2007; Joshi *et al.* 2008; Gordon *et al.* 2009). However, they often focused on few selected technical items, so data are on a limited set of problems (i.e. lack of precision in measurements, sensitivity, specificity, or a particular chemical feature). A quite common finding is the inappropriateness of sophisticated MDs/IVDs when used in tropical conditions.

An additional 18 reports describe suspicions of poor-quality IVDs, mainly from the lay press in Asia, and for half of these (9/18), the subject overlaps with other documents included in this review. In Vietnam, a case of tampering with beta lactate test strips from Roche was reported: the expiry date of the product had been fraudulently altered on the strips themselves, the package inserts and the boxes (they appeared to expire in 2004, when in fact they had expired in 2002). Thanks to the vigilance of the personnel and further investigations, the falsifying of the expiry dates was discovered and the external party responsible for the expiry alterations identified (Day *et al.* 2004). Similar fraud was reported in India for HIV test kits labelled as produced by SD Bioline and Biozyme (People for better treatment 2009). In India, cases of suspected substandard HIV, hepatitis C, dengue kits and other laboratory products were reported (Ludhiana Tribune 2008; The Times of India 2009a,b; Government Accountability Project 2007; BBC news 2006; Outlook India 2008): according to the lay press, allegations were on-going in 2008 that possibly defective tests for blood testing had been authorized despite reports of false-negative results (Chennai online 2008; The Economic Times 2008). Another case, reported in Asia in 2007, involved the distribution of counterfeit glucose test strips, whose genuine producer is Life Scan (Johnson & Johnson). The products spread from China to Canada, the EU, India, Dubai, Turkey, the Philippines, Pakistan and Saudi Arabia (MHRA 2006; Ruder 2007; South Asian Post 2007; Bloomberg 2007; Lifescan 2009).

Five other documents included in the review concern substandard laboratory products in general (The Times of India 2002; Martin *et al.* 2005; Pardeshi 2005; Lumb *et al.* 2006; Newton *et al.* 2006). Two of them propose actions for improving the conditions of laboratory diagnosis in resource-limited countries (Martin *et al.* 2005; Lumb *et al.* 2006).

Finally, we retrieved many papers addressing poor-quality laboratory diagnosis, without clearly distinguishing between poor practices and poor-quality IVDs as the cause (Baker & Porter 1991; Mundy *et al.* 2000; Moore *et al.*

1) Syphilis rapid plasma reagin (RPR) purchased in Tete (Mozambique), January 2007

Screening test for syphilis bought in Tete. The package provides information in two languages, Chinese and English. Information on date of production, lot number, expiry date is provided on the Chinese side only.

2) Malaria rapid test, Benin, May 2007

2. Rock'n'roll, E.P. et al. 1987: Comparative Analysis off the plasmodium falciparum Histidine-Rich Proteins HPR-I HPR-II and HPR-III in Malaria Parasitic off Various Origin. Parasitol, 95,209-227.

Package insert of a malaria rapid diagnostic test purchased in Benin. In the reference section translated from English to French, the author's name "Rock" is replaced by "Rock'n'roll". The underlined words indicate other errors. The correct citation extracted from PubMed is: Rock, E.P. et al. 1987: Comparative analysis of the Plasmodium falciparum histidine-rich proteins HRP-I, HRP-II and HRP-III in malaria parasites of diverse origin. Parasitology; 95, 209-227.

3) Giemsa stock solutions purchased in Kinshasa (Democratic Republic of the Congo (DRC)), December 2008

Three Giemsa stock solutions were purchased from local pharmacies in Kinshasa. Some evident omissions in the packaging were observed as composition and percentage of components are missing; date of manufacturing and expiry dates are not indicated, storage temperature is missing; and hazard symbols are not applied.

4) Aspartate amino transferase (ASAT) test in Kisantu (DRC), May 2010

Test to measure serum concentration of ASAT enzyme purchased at a local pharmacy in Kisantu. Packaging indicates that the enzyme to be measured is alanine amino transferase (ALAT), albeit package insert clearly indicate the correct intended use of the test (ASAT and not ALAT).

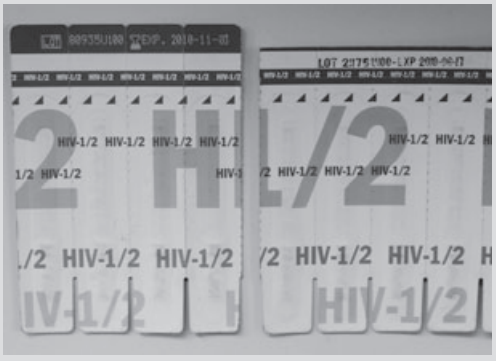
5) Malaria rapid test, South African Republic, June 2010

(a)

(b)

(a) Malaria rapid test used to detect *Plasmodium falciparum* in blood purchased in South Africa. The box and the package insert (not shown) indicate that the product carries a CE marking label. However, the print of CE mark does not comply with the requirements described in Directive 98/79/EC (b). In addition, both the box and the package insert do not display identification and address of the European Union representative (EC-REP). (b) CE marking of conformity as indicated in Directive 98/79/EC. From the Directive: "If the marking is reduced or enlarged the proportions given in the above graduated drawing must be respected".

6) HIV-rapid diagnostic test, Kinshasa (RDC), March 2011



HIV rapid test to detect circulating antibodies against HIV1+2 purchased in Kinshasa. To an inexpert professional, the test on the right side might look perfectly authentic, but it represents an example in which the expiry date was tampered with. Left side: authentic specimen, expiry date and lot number are printed on the upper lid. Right side: upper lid has been cut away, and a falsified expiry date has been stamped on (courtesy of Mr. Samuel Edidi, National AIDS Reference Laboratory, Kinshasa, Congo).

Figure 1 Case reports from field visits.

Table 1 Original reports describing cases reported until 1 January 2011

Date	Commercial name	Type of test	Manufacturer genuine product	Manufacturer/ Distributor of suspected counterfeit/ substandard	Geographical distribution	Classification (peer review journals, grey literature, lay press)	Observed quality problem	Database	Reference
1 June 2001	Various brands	Micro-keratomes	Unspecified	N.D.	Asia	Published article in a peer-review journal	Measurements differ from manufacturer's specifications	PUBMED	Liu & Lam 2001
7 October 2002	N.A.	Sub-standard laboratory	N.A.	N.A.	Asia	Lay press	General referral to substandard practices and use of substandard laboratory products	GOOGLE	The Times of India 2002
1 April 2003	Various brands	Blood glucose meter	Medsys Group Company, Yeongdong Pharm Corp.	N.D.	Africa	Published article in a peer-review journal	Sensitivity, performance, inappropriateness to tropical conditions	BIOLINE	Bimenya *et al.* 2003
10 January 2004	BM-Lactate test strips	BM-Lactate test strips	Roche Diagnostics, Mannheim, Germany	N.D.	Asia	Published article in a peer-review journal	Tampered expiry date	PUBMED	Day *et al.* 2004
19 July 2004	Enzaids HIV1&2 Elisa kit	HIV test kit	Enzaids	N.D.	Asia	Grey literature	Failure in color development	INDIRECT	People for better treatment 2009
26 October 2004	SD Bioline HIV 1&2	HIV test kit	SD Bioline	N.D.	Asia	Grey literature	Failure in color development	INDIRECT	People for better treatment 2009
1 January 2005	Various brands	Various medical devices and IVDs	Unspecified	N.D.	Asia	Published article in a peer-review journal	General referral to the use of low quality products	BIOLINE	Pardeshi 2005
1 May 2005	Unknown	Laboratory	N.D.	N.D.	Developing countries (DCs) in general	Published article in a peer-review journal	Unspecified	INDIRECT	Martin *et al.* 2005
15 July 2005	Various brands	Microscope	Unspecified	N.D.	DCs in general	Published article in a peer-review journal	Unspecified	WISPR5	Lumb *et al.* 2006
2 March 2006	HiMedia, BBL Sensi-Disc	Antibiotic disks for *in-vitro* testing	HiMedia Laboratories, Mumbai; BD Diagnostic Systems, Sparks, Maryland	N.D.	Asia	Published article in a peer-review journal	Opposite results among two brands	GOOGLE	Subhash *et al.* 2006

Table 1 (Continued)

Date	Commercial name	Type of test	Manufacturer genuine product	Manufacturer/ Distributor of suspected counterfeit/ substandard	Geographical distribution	Classification (peer review journals, grey literature, lay press)	Observed quality problem	Database	Reference
1 June 2006	Various brands	Antiseptic	Unspecified	N.D.	South America	Published article in a peer-review journal	Substandard chemical parameters for antimicrobial activity	PUBMED	Volkow *et al.* 2006
1 September 2006	Unknown	Laboratory	Unspecified	N.D.	DCs in general	Published article in a peer-review journal	Unspecified	WISPR5	Newton *et al.* 2006
7 February 2007	One touch ultra test strips	Glucose strips	Life Scan	China	Asia/Middle East	Grey literature	Incorrect units of measurement displayed	INDIRECT	MHRA 2006
12 March 2007	Monobind	Immuno-assay kits	Monobind	ND	Asia/Middle East	Grey literature	Counterfeit immunoassays	INDIRECT	Monobind 2007
1 April 2007		Glucose strips	LifeScan		Asia	Published article in a peer-review journal	Counterfeit test strips	PUBMED	Ruder 2007
24 August 2007	One touch® brand test strips	Glucose strips	Life Scan	Halson Pharmaceutical	Asia/Middle East	Lay press	Fake diabetic kits	INDIRECT	South Asian Post 2007
24 August 2007	ND	Pregnancy, HIV and tuberculosis test kits	ND	Halson Pharmaceutical	Asia/Middle East	Lay press	Fake kits	INDIRECT	South Asian Post 2007
28 September 2007	Unknown	HIV test kit	SD bioline, Biozyme	Monozyme, Ltd.	Asia	Lay press	Counterfeit HIV test kit	INDIRECT	BBC news 2006; Government Account-ability Project 2007
2 July 2007	Various brands	Antibiotic disks	Unspecified	N.D.	South America	Published article in a peer-review journal	Inconsistent results compared with the reference method	BIOLINE	Souza Antunes *et al.* 2007
16 August 2007	One touch	Glucose strips	Life Scan (J&J)	Producer: China (Henry Fu, Halson Pharmaceutical) Distributor: Royal Global Wholesale Corp and Zoe Diagnostics Inc.	Asia/Middle East	Lay press	Counterfeit test strips	GOOGLE	Bloomberg 2007

Table 1 (Continued)

Date	Commercial name	Type of test	Manufacturer genuine product	Manufacturer/ Distributor of suspected counterfeit/ substandard	Geographical distribution	Classification (peer review journals, grey literature, lay press)	Observed quality problem	Database	Reference
30 April 2008	Various brands	Antibiotic disks	Oxoid, HiMedia Laboratories, Span Diagnostics	N.D.	Asia	Published article in a peer-review journal	No reproducible data	BIOLINE	Joshi *et al.* 2008
6 August 2008	Various brands	Fuchsine dye	Unspecified	N.D.	Africa/Asia	Published article in a peer-review journal	Impurity of the powders	WISPR5	Gordon *et al.* 2009
26 October 2008	Unknown	Dengue kit	N.D.	N.D.	Asia	Lay press	Inaccurate results	GOOGLE	Ludhiana Tribune 2008
23 November 2008	Unknown	HIV test kit	N.D.	NACO	Asia	Lay press	Substandard HIV test kit	GOOGLE	Outlook India 2008; Chennai online 2008; The Economic Times 2008
2 April 2009	One Touch	Glucose strips	N.D.	N.D.	Asia	Grey literature	Counterfeit test strips	INDIRECT	Lifescan 2009
13 July 2009	Various brands	HIV kit, Hepatitis C kit, Laboratory products	Unspecified	NACO	Asia	Lay press	Lack of best practices for procurement	GOOGLE	The Times of India 2009a
30 November 2009	Unknown	Preventive kit for viral contamination	ND	ND	Asia	Lay press	Substandard product	GOOGLE	The Times of India 2009b
12 December 2009	Unknown	Medical kits	ND	ND	Asia	Lay press	Substandard product	GOOGLE	Indian Express 2009

Table lists documents retrieved in the literature and fulfilling the following conditions: (i) containing report or suspicion of substandard/counterfeit medical devices (MDs)/*in vitro* diagnostics (IVDs) and (ii) providing information of a country not belonging to the GHTF, which regroups countries with well-defined regulatory systems on MDs/IVDs. Reports are listed in the chronological order of their appearance in the literature. Retrieved information fall, according to the source, into three categories: articles in international peer-reviewed journals, grey literature (conference proceedings, dissertations, theses, or other reports) and lay press (facts in the national or international press). Names of the database are indicated when appropriate or 'indirect' when information was found by looking for articles via references of the primary data.

2001; Dini & Frean 2003; Bates *et al.* 2004; Bretzel *et al.* 2006; Mfinanga *et al.* 2007a,b; Mbembati *et al.* 2008; Van Rie *et al.* 2008).

Reasons behind the paucity of literature on poor-quality MDs/IVDs

Although several field observations and lay press articles suggest that poor-quality MDs/IVDs are quite frequent in limited-resource settings, there are comparably few reports in scientific literature. This discrepancy can be explained by several factors. The poor regulatory oversight in resource-limited settings and the limited awareness of the problem amongst care-givers and decision-makers are manifest in a lack of research and an underreporting in medical journals. Even in the field of medicine, although poor-quality medicines have long been common knowledge and have been officially reported since at least 1912 (FDA Significant Dates in U.S. Food and Drug Law History), a steep increase of scientific reports was only observed after the year 2000 (Caudron *et al.* 2008; Ravinetto *et al.* 2009; WHO 2010a). Additionally, the lack of quality assurance in diagnostic laboratories in most resource-limited settings makes it difficult to trace inherent quality problems of MD/IVDs. Other factors interfering with diagnostic accuracy, such as poor laboratory practices, lack of training and errors in 'end-users' performance, may conceal the role of poor-quality products: in a review on laboratory diagnosis in Africa, poor-quality IVDs were not mentioned amongst the possible causes of inaccurate laboratory diagnosis (Petti *et al.* 2006).

Initiatives to strengthen quality assurance of MDs and IVDs

International initiatives have been put in place to reinforce the access to assured quality MDs and IVDs in resource-limited settings. In 2003, the WHO released the document 'Medical device regulations – Global overview and guiding principles', which provides guidance on quality selection criteria for MDs (notably, the WHO definition of MDs include both MDs and IVDs). This initiative represents an important step towards harmonization worldwide.

Before the WHO, the GHTF (established in 1992) had been promoting harmonized regulations for MDs. It was emulated, in 1996, by the Asian Harmonization Working Party. In 1994, the Pan American Health Organization initiated activities in the field of MD regulations. To our knowledge, no common regulatory initiatives are promoted as of yet amongst African countries.

In 2001, the WHO's Special Program for Research and Training in Tropical Diseases carried out a survey on national regulations for MDs/IVDs. Results showed significant variations in type and stringency of regulations,

Table 2 International programs to guide for selection of medical devices/*in vitro* diagnostics of assured quality

Programme/ project name	Organism promoter	Year started	General objective	Disease	Document released for procurement	Website
Prequalification of diagnostics	WHO	2008	Increase access to diagnostic technologies of assured quality that are appropriate for use in resource limited settings	HIV Hepatitis B Hepatitis C Malaria Chagas	Performance evaluation Performance evaluation Performance evaluation List of prequalified products Performance evaluation	http://www.who.int/diagnostics_laboratory/evaluations/en/
Malaria rapid diagnostic tests (MRDTs) product testing	WHO-FIND	2008	Rank RDTs performance and guide procurement decisions for countries and malaria RDT procurement agencies	Malaria	Performance evaluation rounds 1 & 2 (2008–2009)	http://www.finddiagnostics.org/programs/malaria/find_activities/product_testing/
MRDTs lot testing	FIND	2008	Detect poor performing lots before purchaser organizations/institutions send them to the field	Malaria	Overview document on the testing process	http://www.finddiagnostics.org/programs/malaria/find_activities/lot_testing/
The sexually transmitted diseases diagnostics initiative (STDDI)	WHO STDDI	1994	Promote the development, evaluation and application of diagnostic tests for sexually transmitted infections appropriate for developing countries.	STI	Laboratory-based evaluation of rapid syphilis diagnostics	http://www.who.int/std_diagnostics/

with most resource-limited countries – mainly in Africa (11 of 15 answering the survey), the Americas (9/18) and the Western Pacific Area (15/22) – lacking any specific regulation (WHO 2001). Since then, the situation has improved in Asia and in the Western Pacific Area, whilst in Africa, only Egypt, Kenya and South Africa have Amendment Acts for MDs (Emergo 2011a). Next to international regulations, a number of disease-specific initiatives were launched over the last years to provide practical guidance for selection of IVDs of assured quality (Table 2).

The CE mark and FDA compliance label for IVDs

In some countries, such as Egypt, South Africa, Argentina, Brazil, Mexico, Peru and Venezuela, in the absence of specific national requirements, the common practice for some imported products is to request evidence of EU (CE mark) or US (FDA compliance, FDA 2011) quality labels (Emergo 2011a). The WHO supports this strategy (WHO 2003); however, the regulatory authority of the recipient country should check these labels with the body, which granted the certificate, as is done by the Egyptian health authorities (Emergo 2011b).

However, the significance of the CE mark or FDA compliance is limited for some IVDs. A full quality evaluation (including diagnostic accuracy and lot-testing prior to release) is requested for the CE mark only for products considered at 'high risk' in 'Annex II' of the 98/79 EU Directive (European Commission 2011a, annex A and B). This applies, for instance, to HIV diagnostic tests. By contrast, for IVDs not listed in the Annex II – such as malaria rapid diagnostic tests and IVDs for other parasitic diseases – the CE mark is obtained by filling in a technical file and a declaration of conformity by the manufacturer (European Commission 2011a), rendering the acquisition of the CE marking label to a purely administrative process. The EU could strengthen the regulatory oversight of those products, which are highly needed in resource-poor settings (Mori *et al.* 2010; Gillet *et al.* 2011), by including them in 'Annex II' of the 98/79 Directive. Recently, the U.S. FDA assessments on the 510(k) premarket process (products not in the highest class of risk) had been under review to facilitate innovation initiatives and face unmet public health needs (Roehr 2010). It is hoped that this will lead to an improvement of the review process that can be beneficial also in terms of quality assurance for resource-limited countries (Mori *et al.* 2010). The EU is also currently revising the Medical Devices Directives (European Commission 2011b) and will probably implement the GHFT risk classification of IVDs. This classification considers the diagnostic information of an IVD as well as the impact of its results (whether true or false) to the individual and the public health (GHTF 2008a). From the GHFT perspective, most IVDs for tropical infectious diseases (such as malaria rapid diagnostic tests) fit into Class C, which corresponds to a moderate public health risk or a high individual risk, whereas HIV screening tests fit into Class D, which corresponds to high individual and high public health risk. The GHFT proposes that both Class C and D IVDs require premarket review by a regulatory authority assessing the quality management system of the manufacturer and the technical specifications of each product, with differences in the level of details and depth between Class C and Class D (GHTF 2008b). If the requirements, particularly those for Class C IVDs, are strict enough, this revision could represent a significant step towards supporting countries with weak regulatory supervision.

Open issues: definitions of substandards, harmonized testing, surveys of MDs/IVDs

To evaluate the extent of poor-quality MDs/IVDs, harmonized operational definitions are required, as is already done in the field of medicine. Such clear-cut definitions would facilitate identification of poor-quality products in distribution channels and aid in the design and implementation of appropriate regulations. However, defining substandards and counterfeits in the field of MDs/IVDs is less straight forward than in medicine, because 'standards' are often less clearly described.

Guidelines for performance testing exist only for a few IVD technologies and harmonized methods for performance testing in reference and field settings should be further developed (Banoo *et al.* 2006; Bell & Peeling 2006; Herring *et al.* 2006a,b; Peeling *et al.* 2006; Stevens *et al.* 2008). The work of WHO (2011d) and other groups (El-Safi *et al.* 2003; Boelaert *et al.* 2004; Gidwani *et al.* 2009; Otani *et al.* 2009; Gillet *et al.* 2010) on performance testing of MDs/IVDs should continue and be extended to MDs/IVDs for other diseases. In parallel, standardization of IVDs performance requires the establishment of common biological materials (biological references) and methods for parasitic diseases to share a uniform 'performance testing language' and to compare results generated by different groups (WHO 2011c).

Sustainable investments are needed to create or strengthen national regulatory oversights on MDs/IVDs and to encourage a proactive and transparent exchange of information between Northern and Southern regulatory authorities. *Ad hoc* surveys on the quality of MDs/IVDs could help to increase awareness amongst care-givers, decision-makers and the scientific community, as is the case in the field of medicines.

Conclusion

Because of poor regulatory supervision, amongst other factors, patients in resource-limited countries are potentially exposed to the risk of poor-quality MDs and IVDs. Informal field observations support this view, but they are not confirmed by scientific literature; therefore, one can argue that although poor-quality MDs/IVDs are present, they are likely underreported in resource-poor settings. Current international initiatives to strengthen quality assurance of MDs/IVDs are not sufficient to prevent this risk. A more comprehensive approach is needed, including pre-established definitions of substandards and counterfeits, documentation of the extent of the problem via *ad hoc* quality surveys, North–South collaboration to share best-practices and regulatory and technical information and enforcement of stringent regulatory oversight for products highly needed in resource-poor settings. It is hoped that such a comprehensive approach would help to reduce the North–South gap in access to MDs/IVDs of assured quality.

Acknowledgements

We thank our colleagues for informal communication on this topic and Gillet Philippe for helpful discussions and advice. Acknowledgements go to Dr. Hooghe Robert, Prof. Elizabeth Hooghe-Peters and Annelies Scheirlinck for the critical reading of the manuscript. Special thanks go to Elizabeth Toomer of Lost in Translation (http://www.lost-in-translation.be) for her essential work in editing our manuscript.

References

Baker ME & Porter FR (1991) A report on radiology at Muhimbili Medical Center, Dar es Salaam, Tanzania. *American Journal of Roentgenology* **157**, 195.

Banoo S, Bell D, Bossuyt P *et al.* (2006) Evaluation of diagnostic tests for infectious diseases: general principles. *Nature Reviews Microbiology* **4** (Suppl. 9), S21–S31.

Bates I, Bekoe V & Asamoa-Adu A (2004) Improving the accuracy of malaria-related laboratory tests in Ghana. *Malaria Journal* **3**, 38.

BBC news (2006) Two accused over 'fake' HIV tests. http://news.bbc.co.uk/2/hi/south_asia/6099064.stm (last accessed date 12 April 2011).

Bell D & Peeling RW (2006) Evaluation of rapid diagnostic tests: malaria. *Nature Reviews Microbiology* **4** (Suppl. 9), S34–S38.

Bimenya GS, Nzarubara GR, Kiconco J, Sabuni S & Byarugaba W (2003) The accuracy of self monitoring blood glucose meter systems in Kampala Uganda. *African Health Sciences* **3**, 23–32.

Bloomberg (2007) *China Counterfeit Diabetes Tests Tracked by J&J (Update1)*. http://www.bloomberg.com/apps/news?pid=20670001&sid=aCAuLKG2YwKc (last accessed date 12 April 2011).

Boelaert M, Rijal S, Regmi S *et al.* (2004) A comparative study of the effectiveness of diagnostic tests for visceral leishmaniasis. *American Journal of Tropical Medicine and Hygiene* **70**, 72–77.

Bonnet M, Gagnidze L, Varaine F, Ramsay A, Githui W & Guerin PJ (2009) Evaluation of FASTPlaqueTB to diagnose smear-negative tuberculosis in a peripheral clinic in Kenya. *The International Journal of Tuberculosis and Lung Disease* **13**, 1112–1118.

Bretzel G, Siegmund V, Nitschke J *et al.* (2006) External quality assurance for the laboratory diagnosis of Buruli ulcer disease in Ghana. *Tropical Medicine & International Health* **11**, 1688–1693.

Caudron JM, Ford N, Henkens M, Mace C, Kiddle-Monroe R & Pinel J (2008) Substandard medicines in resource-poor settings: a problem that can no longer be ignored. *Tropical Medicine International Health* **13**, 1062–1072.

Chennai online (2008) *NACO Pulled up for Substandard HIV Kits in Country*. http://news.chennaionline.com/newsitem.aspx?NEWSID=51b71860-3a4b-4730-970c-d24a168b1836&CATEGORYNAME=NATL (last accessed date 12 April 2011).

Day JN, Hien TT & Farrar J (2004) Expiry-date tampering. *Lancet* **363**, 172.

Dini L & Frean J (2003) Quality assessment of malaria laboratory diagnosis in South Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **97**, 675–677.

El-Safi SH, Abdel-Haleem A, Hammad A *et al.* (2003) Field evaluation of latex agglutination test for detecting urinary antigens in visceral leishmaniasis in Sudan. *Eastern Mediterranean Health Journal* **9**, 844–855.

Emergo (2011a) *Worldwide Medical Device Regulations*. http://www.emergogroup.com/resources/worldwide-medical-device-regulations (last accessed date 12 April 2011).

Emergo (2011b) *Medical Device Regulatory Requirements for Egypt*. http://www.emergogroup.com/files/Egypt-USDOC-Analysis.pdf (last accessed date 12 April 2011).

European Commission (2011a) *Medical Devices Current Legislation*. http://ec.europa.eu/enterprise/sectors/medical-devices/regulatory-framework/legislation/ (last accessed date 12 April 2011).

European Commission (2011b) *Revision of the Medical Device Directives*. http://ec.europa.eu/consumers/sectors/medical-devices/documents/revision/index_en.htm (last accessed date 27 June 2011).

FDA (2011) *Overview of IVD Regulation*. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm123682.htm (last accessed date 12 April 2011).

FDA. *Significant Dates in U.S. Food and Drug Law History*. http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm (last accessed date 12 April 2011).

GHTF (2008a) *Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices*. http://www.ghtf.org/documents/sg1/sg1final_n046.pdf (last accessed date 27 June 2011).

GHTF (2008b) *Principles of In Vitro Diagnostic (IVD) Medical Devices Classification*. http://www.ghtf.org/documents/sg1/sg1final_n045.pdf (last accessed date 27 June 2011).

Gidwani K, Rai M, Chakravarty J, Boelaert M & Sundar S (2009) Evaluation of leishmanin skin test in Indian visceral leishmaniasis. *American Journal of Tropical Medicine and Hygiene* **80**, 566–567.

Gillet P, Mukadi P, Vernelen K *et al.* (2010) External quality assessment on the use of malaria rapid diagnostic tests in a non-endemic setting. *Malaria Journal* **9**, 359.

Gillet P, Maltha J, Hermans V, Ravinetto R, Bruggeman C & Jacobs J (2011) Malaria rapid diagnostic kits: quality of packaging, design and labelling of boxes and components and readability and accuracy of information inserts. *Malaria Journal* **10**, 39.

Gordon C, Van Deun A & Lumb R (2009) Evaluating the performance of basic fuchsin for the Ziehl-Neelsen stain. *International Journal of Tuberculosis and Lung Disease* **13**, 130–135.

Government Accountability Project (2007) *World Bank Funding Use of Defective HIV-Testing Kits*. http://www.commondreams.org/news2007/0928-03.htm (last accessed date 12 April 2011).

Herring A, Ballard R, Mabey D, Peeling RW, WHO, Diag TSTD (2006a) Evaluation of rapid diagnostic tests: syphilis. *Nature Reviews Microbiology* **4** (Suppl. 12), S33–S40.

Herring A, Ballard R, Mabey D, Peeling RW, WHO, Diag TSTD (2006b) Evaluation of rapid diagnostic tests: chlamydia and gonorrhoea. *Nature Reviews Microbiology* **4** (Suppl. 12), S41–S48.

Indian Express (2009) *In the house*. http://www.indianexpress.com/news/in-the-house/553186/ (last accessed date 12 April 2011).

Joshi A, Iyer V, Balasubramaniam U, Kagal A & Bharadwaj R (2008) Comparison of efficacy of three commercially available antibiotic discs. *Indian Journal of Medical Microbiology* **26**, 160–162.

Lifescan (2009) *Counterfeit OneTouch Test Strip Alert*. http://www.lifescan.com/company/about/press/counterfeit/ (last accessed date 12 April 2011).

Liu KY & Lam DS (2001) Direct measurement of microkeratome gap width by electron microscopy. *Journal of Cataract & Refractive Surgery* **27**, 924–927.

Ludhiana Tribune (2008) *Dengue Outbreak 'Benefits' Docs, Labs*. http://www.tribuneindia.com/2008/20081125/ldh1.htm (last accessed date 12 April 2011).

Lumb R, Van Deun A, Kelly P & Bastian I (2006) Not all microscopes are equal. *International Journal of Tuberculosis and Lung Disease* **10**, 227–229.

Martin R, Hearn TL, Ridderhof JC & Demby A (2005) Implementation of a quality systems approach for laboratory practice in resource-constrained countries. *Aids* **19**(Suppl 2), S59–S65.

Mbembati NA, Mwangu M, Muhondwa EP & Leshabari MM (2008) Performance indicators for quality in surgical and laboratory services at Muhimbili National Hospital (MNH) in Tanzania. *East African Journal of Public Health* **5**, 13–16.

Mfinanga GS, Mutayoba B, Mbogo G *et al.* (2007a) Quality of HIV laboratory testing in Tanzania: a situation analysis. *Tanzania Health Research Bulletin* **9**, 44–47.

Mfinanga GS, Ngadaya E, Mtandu R *et al.* (2007b) The quality of sputum smear microscopy diagnosis of pulmonary tuberculosis in Dar es Salaam, Tanzania. *Tanzania Health Research Bulletin* **9**, 164–168.

MHRA (2006) *MDA/2006/070-LifeScan OneTouch Ultra, LifeScan InDuo and LifeScan PocketScan Blood Glucose Meters*. http://www.mhra.gov.uk/PrintPreview/DefaultSP/CON2025512 (last accessed date 12 April 2011).

Monobind (2007). *Counterfeit Monobind Test Kits*. http://www.monobind.com/site/counterfiet-packaging.html (last accessed date 12 April 2011).

Moore A, Herrera G, Nyamongo J *et al.* (2001) Estimated risk of HIV transmission by blood transfusion in Kenya. *Lancet* **358**, 657–660.

Mori M, Ravinetto R & Jacobs J (2010) *FDA Seeks to Modify Regulation of Medical Devices: Challenges for Resource-Poor Settings? Rapid Response at BMJ.com*. http://www.bmj.com/content/341/bmj.c4415.extract/reply#bmj_el_241501 (last accessed date 12 April 2011).

Mundy C, Ngwira M, Kadewele G, Bates I, Squire SB & Gilks CF (2000) Evaluation of microscope condition in Malawi. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **94**, 583–584.

Newton PN, Green MD, Fernandez FM, Day NP & White NJ (2006) Counterfeit anti-infective drugs. *Lancet Infectious Diseases* **6**, 602–613.

Otani MM, Vinelli E, Kirchhoff LV *et al.* (2009) WHO comparative evaluation of serologic assays for Chagas disease. *Transfusion* **49**, 1076–1082.

Outlook India (2008) *NACO Pulled up for Substandard HIV Kits in Country*. http://www.pbtindia.com/Media/Outlook%20Nov%5B1%5D.%202008%20(HIV%20kits).pdf (last accessed date 12 April 2011).

Pardeshi GS (2005) Medical equipment in government health facilities: missed opportunities. *Indian Journal of Medical Sciences* **59**, 13–19.

Peeling RW, Smith PG & Bossuyt PMM (2006) A guide for diagnostic evaluations. *Nature Reviews Microbiology* **8** (Suppl. 12), S2–S6.

People for better treatment (2009) *Medical Negligence" of Another Kind: Use of Defective HIV Kits*. http://www.pbtindia.com/Anuradha_Story/Anu_5.htm (last accessed date 12 April 2011).

Petti CA, Polage CR, Quinn TC, Ronald AR & Sande MA (2006) Laboratory medicine in Africa: a barrier to effective health care. *Clinical Infectious Diseases* **42**, 377–382.

Ravinetto RM, Cloez S, Scouflaire-Mallet SM & Vandenbergh D (2009) Poor-quality medicines in developing countries. *Lancet Infectious Diseases* **9**, 267–268.

Roehr B (2010) FDA seeks to modify regulation of medical devices. *British Medical Journal* **341**, c4415. doi:10.1136/bmj.c4415.

Ruder K (2007) Additional counterfeit tests strips found. *Diabetes Forecast* **60**, 29.

South Asian Post (2007) *Fake Diabetic Kit Alert*. http://classifieds.asianpacificpost.com/portal2/ff80808114994add0114998837430013_Fake_diabetic_kit_alert.do.html (last accessed date 12 April 2011).

Souza Antunes AL, Secchi C, Reiter KC, Rodrigues Perez LR, Peixoto de Freitas AL & Alves d'Azevedo P (2007) Evaluation of oxacillin and cefoxitin disks for detection of resistance in coagulase negative staphylococci. *Memórias do Instituto Oswaldo Cruz* **102**, 719–723.

Stevens W, Gelman R, Glencross DK, Scott LE, Crowe SM & Spira T (2008) Evaluating new CD4 enumeration technologies for resource-constrained countries. *Nature Reviews Microbiology* **6**, S29–S38.

Subhash CA, Agarwal N & Agarwal S (2006) Comparison of two amoxicillin/clavulanic acid-resistant profiles employing two types of assay disks: a pilot study in 50 isolates from a tertiary care hospital in India. *Current Therapeutic Research* **67**, 151–156.

The Economic Times (2008) *NACO Pulled up for Substandard HIV Kits in Country*. http://economictimes.indiatimes.com/articleshow/3748209.cms (last accessed date 12 April 2011).

The Times of India (2002) *No Tests to See if a Pathology Lab is Accurate*. http://timesofindia.indiatimes.com/articleshow/24401257.cms (last accessed date 12 April 2011).

The Times of India (2009a) *Diagnostic Kits Cleared by Testing Agency Despite Ban*. http://timesofindia.indiatimes.com/NEWS-India-Diagnostic-kits-cleared-by-testing-agency-despite-ban/articleshow/4770522.cms (last accessed date 12 April 2011).

The Times of India (2009b) *Row Over Supply of Preventive Kit*. http://m.timesofindia.com/PDATOI/articleshow/5282353.cms (last accessed date 12 April 2011).

U.S. FDA. *Recalls, Market Withdrawals, & Safety Alerts*. http://www.fda.gov/safety/recalls/default.htm (last accessed date 12 April 2011).

Van Rie A, Fitzgerald D, Kabuya G *et al.* (2008) Sputum smear microscopy: evaluation of impact of training, microscope distribution, and use of external quality assessment guidelines for resource-poor settings. *Journal of Clinical Microbiology* **46**, 897–901.

Visiongain (2008) http://www.visiongain.com/Report/392/In-Vitro-Diagnostics-Market-Analysis-2009-2024 (last accessed date 12 April 2011).

Volkow P, Sandoval S, Campos AM *et al.* (2006) Increase in catheter insertion-site infections associated to the introduction of a substandard competitive antiseptic. *American Journal of Infection Control* **34**, 335–337.

WHO (2001) *Diagnostics for TB: Global Demand and Market Potential. Annex: Regulation of In Vitro Diagnostics: A Global Perspective*. TBDI.04.1 http://www.who.int/tdrold/publications/publications/pdf/tbdi/tbdi_annex.pdf (last accessed date 12 April 2011).

WHO (2003) *Medical Device Regulations: Global Overview and Guiding Principles*. http://www.who.int/medical_devices/publications/en/ (last accessed date 12 April 2011).

WHO (2010a) *Assessment of Medicines Regulatory Systems in Sub-Saharan African Countries: An Overview of Findings from 26 Assessment Reports*. http://apps.who.int/medicinedocs/en/m/abstract/Js17577en/ (last accessed date 12 April 2011).

WHO (2010b) *Fact Sheet N°275, Revised in January 2010*. http://www.who.int/mediacentre/factsheets/fs275/en/index.html (last accessed date 12 April 2011).

WHO (2011a) *Counterfeit Medicines: Frequently Asked Questions. What are Counterfeit Medicines?* http://www.who.int/medicines/services/counterfeit/faqs/03/en/index.html (last accessed date 12 April 2011).

WHO (2011b) *Counterfeit Medicines: Frequently Asked Questions. What are Substandard Medicines?* http://www.who.int/medicines/services/counterfeit/faqs/06/en/index.html (last accessed date 12 April 2011).

WHO (2011c) *Expert Committee on Biological Standardization*. http://www.who.int/biologicals/areas/en/ (last accessed date 12 April 2011).

WHO (2011d) *WHO Prequalification of Diagnostics Programme*. http://www.who.int/diagnostics_laboratory/evaluations/en/ (last accessed date 12 April 2011).

Zarocostas J (2010) WHO calls for better access to medical devices in poor nations. *British Medical Journal* **341**, c5052. doi:10.1136/bmj.c5052.

Corresponding Author **Marcella Mori,** Unit of Tropical Laboratory Medicine, Prince Leopold Institute of Tropical Medicine (ITM), Nationalestraat 155, 2000 Antwerp, Belgium. Tel.: +32 3 247 07 45; Fax: +32 3 247 64 40, E-mail: marcellamori@gmail.com