In vitro diagnostics: international regulation, and quality in resource limited settings

Raffaella Ravinetto & Jan Jacobs
QUAMED - Institute of Tropical Medicine Antwerp
12th July 2017
1. Quality of IVDs in low-resource settings: under the radar...

Laboratory Medicine in Africa: A Barrier to Effective Health Care

Reasons for poor laboratory performance:
- Clinical (mis)diagnosis, distrust and under-use of lab
- Inadequate health care infrastructure
- Lack of trained and competent staff
- Weaknesses of health systems
- Lack of water, power, equipment, procedures
- Problems with IVDs NOT mentioned!

IVD quality not mentioned
No awareness, no data
But do we need to care about it?

Reasons for poor laboratory performance:
• 60% of errors are preanalytical, 25% postanalytical, only **15% is analytical** Plebani2009, WHO2011
• ! Infrastructure, health systems, staff education,.....

Three good reasons to care about quality of IVD:
• ! patient care
• ! guidelines, surveillance, algorithms malaria, HIV, tuberculosis, antibiotic stewardship...
• ! confidence of professionals/authorities/public
The role of national reference laboratories ..... example of Benin
Example on how a reference lab can guide

Wide variation in disk quality in 16 selected disks from nine manufacturers.

EUCAST Development Laboratory (EDL)
Växjö
Sweden

23 October 2015

- The disks were chosen either because of their central role in the EUCAST disk testing system (e.g. screening disks for important resistant mechanisms), or because problems have been detected by the EUCAST Development Laboratory (EDL) or other laboratories.
### Side-to-side evaluations of IVDs improve quality over time

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Disk content (µg)</th>
<th>Range</th>
<th>Bio-Rad</th>
<th>Biolo-fichem</th>
<th>BD</th>
<th>Abtek</th>
<th>SirScan</th>
<th>Oxoid</th>
<th>HiMedia</th>
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<tbody>
<tr>
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<td>L</td>
<td>H</td>
<td>H</td>
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<td>H</td>
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<td>H</td>
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<td>NA</td>
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<td>L</td>
<td>H</td>
<td>H</td>
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<td>L*</td>
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<td>H</td>
<td>L</td>
<td>L</td>
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</table>

**Mean value within ± 1 mm of the target value**

**Mean value >1 mm but within ± 2 mm of the target value**

**Mean value >2 mm from target value but still within the QC range**

**Mean value out of the QC range**

NA = Not Available

H = High, mean value >1 mm above target

L = Low, mean value >1 mm below target

* One or more readings out of QC range
Risk classification of IVDs
(International Medical Device Regulators Forum, www.imdrf.com)

TABLE 1: General classification of IVDD.

<table>
<thead>
<tr>
<th>Class</th>
<th>Individual risk</th>
<th>Public health risk</th>
<th>Examples</th>
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<tr>
<td>B</td>
<td>••</td>
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<td>C</td>
<td>••</td>
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<tr>
<td>D</td>
<td>•••</td>
<td>•••</td>
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</table>

(*) Low, (**) moderate, and (***) high.
CE mark is not always a guarantee for intrinsic quality.
Examples: Falsification rare, small-scale, anecdotal (scale, profit margin)
Examples: Falsification

- Counterfeit reagents aren’t on sale in busy public markets.....

- .... In 2012, researchers in London and Białystok, Poland, reported using an antibody-based kit, called an ELISA, to detect a certain protein in the blood of people with chronic kidney disease.

- But when kidney-disease specialist Herbert Lin of Massachusetts General Hospital in Boston purchased the same kit — branded as a product of USCN Life Science in Wuhan, China — and subjected it to rigorous testing, he found that it targeted another protein....
**CAAMEKI ASBL**

Bâtiment Zone de santé Kisantu N° impôt A1005851 X  
Tél. : 0999226791 / 0815998710 - E-mail : caameki@yahoo.fr  
Compte Bancaire : -01 101-1003734-49 / USD - BCDC LIMETE

**FACTURE**

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<td>Comptant</td>
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<tr>
<td>Document libellé en</td>
<td>Dollar US</td>
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<td>A payer avant le</td>
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<td>Code</td>
<td>CLEXC</td>
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**CLIENT EXCEPTIONNEL**

KINSHASA  
KINSHASA  
KINSHASA  
Congo

<table>
<thead>
<tr>
<th>Référence</th>
<th>Désignation</th>
<th>Unité</th>
<th>Quantité</th>
<th>Prix Unitaire</th>
<th>% Rem.</th>
<th>Montant H.T.</th>
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</tbody>
</table>
Falsification

Tampering / of expiry date
Falsification – some hints about het CE mark

Symbol outlines
European Representative (address)
Hints about the CE mark

INSTI™ HIV-1/HIV-2 Antibody

Intended for single use determination of HIV-1/HIV-2 antibodies in whole blood, serum, or EDTA plasma.

For in vitro diagnostic use only.
No refrigeration required. Optimum storage conditions 15-30°C.
Consult instructions for use.
Do not reuse.

Harmful if swallowed.

Contents:
1. Membrane Unit
1. Sample Diluent
1. Color Developer
1. Clarifying Solution
1. Single-use Pipet
1. Lancet STERILE
1. Alcohol Swab
1. Instructions for Use

INSTITUTE OF TROPICAL MEDICINE ANTWERP
Substandards common and large scale

External quality assessment of malaria microscopy in the Democratic Republic of the Congo

Pierre Mukadi1, Philippe Giller2, Albert Lukuka3, Ben Atua3, Simelo Kahodi4, Jean Lokombe4,5, Jean-Jacques Muyembe1,5 and Jan Jacobs6,7

Correct dimensions (> 1 cm) and thickness of the film 110 (71.0%)
Complete hemolysis of the red blood cells 118 (76.1%)
No Giemsa stain precipitates observed 60 (38.7%)
Good contrast between nucleus and cytoplasm 70 (45.1%)
Complies with all criteria mentioned above 30 (19.4%)
Substandards

Non-tropicalized package

Note:

CE mark focuses on the European Community
- Climate, infrastructure
- Population assessed
- End-user’s level!
- Lab/Clinician’s interphase
Substandards

Pressure on price – volumes – lead times
Assessment of desiccants and their instructions for use in rapid diagnostic tests

Barbara Barbé¹, Philippe Gillet², Greet Beelaert², Katrien Fransen² and Jan Jacobs¹*
Procurement and Supply

Errors
Product codes too similar
No alert from the manufacturer

Four different malaria RDT brands were used (not specified for 11.5% of health facilities): (i) Paracheck Pf-Rapid Test (Orchid Biomedical Systems, Goa, India, 77/680, 11.3%); (ii) SD malaria Ag Pf/Pan (394/680, 57.9%) which is the RDT actually recommended by the PNLP; (iii) **SD Malaria antigen Pf/Pv** (Standard Diagnostics, Inc., Kyonggi-do, Korea, 99/680, 14.6%) and; (iv) SD Malaria antigen Pf (32/680, 4.7%). SD Malaria antigen Pf/Pv exclusively circulated in Kasai Occidental and Sud Kivu where it was used in half of the participating health facilities (respectively 62/126 and 37/71), while in Maniema only Paracheck Pf-Rapid Test was used (22/24).
Procurement and supply  What we ordered and what we received

Labeling is part of the IVD risk mitigation
At the present... malaria is diagnosed by looking for the parasites in a drop of blood.

At the most recent... diagnostic issues are the detection of malaria antibodies by immunoassay.
Laboratorians and clinicians often rely on package inserts of diagnostic tests to assess their accuracy. We compared test accuracy for tuberculosis diagnostics reported in 19 package inserts against estimates in published meta-analyses and found that package inserts generally report overoptimistic accuracy estimates. However, package inserts of most tests approved by the U.S. Food and Drug Administration (FDA) or endorsed by the World Health Organization provide more realistic estimates that agree with meta-analyses.
Retrospective evaluation of immunochromatographic Salmonella diagnostic tests for the rapid detection of Salmonella serovars in blood culture fluid

L.M.S. Kuijpers, P. Chung, B. Barbe, C. Khamb, J. Jacobs
1Institute of Tropical Medicine, Antwerp, Belgium, 2Department of Microbiology and Immunology, KU Leuven, Belgium, 3Sihanouk Hospital Centre of HOPE, Phnom Penh, Cambodia

(Serum/Stool)

Sensitivity: S.typhi-S.paratyphi assay was run using serum and stool samples versus culture positive samples and found to give positive results in all cases.

BIBLIOGRAPHY

Poor or wrong information
Lack of Harmonization
Hidden errors, brand names and types

One product is lacking
Sodium Biselinite = the selective component!
Ornithine decarboxylase, 216 USD/vial, Cambodia not properly working
ISO attitude (ISO15189 - ISO13485)

Non-advertised change of product name
ISO attitude (see next speakers)

Manufacturers not yet client-related
  Handling of customer complaints (see next speaker)
  Good-will but unfamiliar with the field/customer

Distributors
  Knowledge and mastering ("fournisseurs ambulants")
  Sales practices?
  Stock management (customs, payments...)

Special for IVDs: Rebranders

Renault Trafic  Opel Vivaro  Nissan Cabstar
ISO attitude (ISO15189 - ISO13485)

Dear Barbara,
We did have validation done on the change. As I mentioned the in-house validation is usually limited and full evaluation would be required at customers end. If you are not comfortable with the new reading time simply disregard the new version of the package insert.”

TEST PROCEDURE (see illustration 1)
Allow test card, reagent, specimen, and controls to equilibrate to room temperature (15-30°C) before testing. Place the test card on a clean and level surface.

Test Procedure for Serum or Plasma Specimen:
1. Hold the conjugate dropper bottle vertically and transfer 2 full drops (~100 µL) of conjugate into the reagent port (marked “R”). Wait for the conjugate to pass the sample port (marked “S”) as indicated by the red liquid front passing through.
2. Transfer 5 µL of sample (serum, plasma or treated whole blood specimen) onto the membrane in the sample port at the bottom of the rectangular test window of the test card.
3. Read result between 10-15 minutes after the sample application. Do not attempt to interpret result after 15 minutes.

TEST PROCEDURE (Please refer to Illustration 1.)
• Allow test card, reagent, specimen, and controls to equilibrate to room temperature (15-30°C) before testing.
• Place the test card on a clean and level surface.

Test Procedure for Serum and Plasma Specimen:
1. Hold the conjugate dropper bottle vertically and transfer 2 full drops (~100 µL) of conjugate into the reagent port (marked “R”). Wait for the conjugate to pass the sample port (marked “S”) as indicated by the red liquid front passing through.
2. Transfer 5 µL of sample onto the membrane in the sample port.
3. Read result within 5 minutes after the sample application. Do not attempt to interpret result after 10 minutes.

VIEWPOINTS
Rapid Diagnostic Tests for Neglected Infectious Diseases: Case Study Highlights Need for Customer Awareness and Postmarket Surveillance

Barbara Barbé1, Kristien Verdonck1,4, Seyda El-Safi2, Basudha Khanal3, Syna Teav4, Jean-Roger Lilo Kalo5, Raffaella Ravinetti1, François Chappuis7, Marleen Boelaert1, Jan Jacobs1,4

INSTITUTE OF TROPICAL MEDICINE ANTWERP
Diagnostic Stewardship

The right IVD for the right indication

Education (including CME)
Training
Know what is behind the choice

The diagnosis of typhoid fever in the Democratic Republic of the Congo

Octavie Lunguya a,b, Marie-France Phoha a,b, Steve Ahuka Mundeko a,b, Edmonde Bonebe a, Pierre Mukadi a, Jean-Jacques Muyembe a,b, Jan Verhaegen c, Jan Jacobs d,*

a National Institute for Biomedical Research, Kinshasa, the Democratic Republic of the Congo
b University Hospital of Kinshasa, the Democratic Republic of the Congo
c University Hospital Leuven, Leuven, Belgium
d Institute of Tropical Medicine, Nationalestraat 155, B-2000, Antwerp, Belgium

An EQA on the Widal test consisting of three samples revealed correct scores by respectively 27.1%, 65.6% and 3.1% of 125 participating laboratories. Most (80.9% of 152 laboratories) performed <100 Widal tests per month, with a median sample positivity rate of 32.6% (range 0–90.7%). The Widal test was mostly performed on a single sample and by slide agglutination (89.5% and 97.0% respectively); errors in cold chain and procedures were recorded (not making serial dilutions, estimating titres by the intensity of agglutination). Among 293 prescribers, 52.2% and 40.8% requested the Widal test for treatment follow-up and detection of chronic carriers respectively.

Note: External Quality Assessment, reference laboratories
Note: External Quality Assessment – support from the North

- For-free use of validated EQA panels provided by the Belgian reference lab
- Learning moments about practices and problems of diagnostic laboratories
Diagnostic Stewardship

Why are inaccurate tuberculosis serological tests widely used in the Indian private healthcare sector? A root-cause analysis

Szymon Jaroslawski a, Madhukar Pai b,*

a Institute of Bioinformatics and Applied Biotechnology, Bangalore, India
b McGill University, Montreal, Canada

Received 14 October 2011; received in revised form 24 November 2011; accepted 9 December 2011
Available online 1 February 2012

referral fees (incentives) which encourage the use of serodiagnostics. Doctors who request serological tests are often offered by the private laboratories about 20–50% of the price (i.e., between 150 and 300 rupees) paid by the patient.
Take-home messages about quality of IVD in low resource settings

1. **Scope/Extent and Awareness** are still limited, but it exists and is a problem

2. There are many “faces” of poor quality of IVDs:
   - Falsification small-scale and rare, **Substandards** common and large-scale
   - Procurement and Supply is a cause of error
   - Costs and prices may influence (tenders, private sector)
   - IVD instructions for use poor and/or too optimistic
   - Failing ISO attitude among manufacturers, distributors and customers
   - **Diagnostic Stewardship** needs to be developed and disseminated

3. **Professional Societies in the North** can efficiently contribute:
   - verifications, product assessments, (external) quality control, awareness, diagnostic stewardship
WHO Prequalification of in vitro diagnostics
WHO Prequalification of in vitro diagnostics

- Review of a product dossier
- Laboratory evaluation of performance and operational characteristics
- Manufacturing site(s) inspection.
- Post-market surveillance is a WHO post-qualification activity which includes reactive and proactive measures:
  - complaint reporting
  - post-shipment/pre-distribution lot testing
  - mandatory manufacturer notification of changes to the product or the quality management system.
WHO Prequalification of in vitro diagnostics

Pre-submission form

Priority product
  Yes
  No

Dossier screening

Dossier complete

Dossier review
Site inspection
Laboratory evaluation

Prequalification decision

Figure 1 Prequalification of diagnostics: full assessment process
WHO Prequalification of in vitro diagnostics

- Applications to the WHO PQ must come from the legal manufacturer
- Several manufacturers purchase finalized/semi-finalized products, and then "re-brand" and market them under their own name/brand
- WHO considers a "re-branded" product to be one that is manufactured under identical conditions at the same manufacturing site(s) as the original product.
- A “re-branded” product is identical in every aspect to the product by the original manufacturer, except that it is labeled with the "re-branded" product name and purchaser identifier.
- WHO encourages joint applications by original manufacturers and "re-branders". Both must consent to the public disclosure of this "re-branding" arrangement
Some good news: WHO Global Model Regulatory Framework for Medical Devices including in vitro diagnostic medical devices

- WHO Expert Committee on Specifications for Pharmaceutical Preparations, 2016
- Guidance and support to develop/implement regulatory controls relating to medical devices....
- A progressive, or stepwise, approach to regulating the quality, safety and performance of medical devices.....
- A staged development, from basic-level controls toward expanded-level controls, e.g. inspection of registered establishments and oversight of clinical investigations.
Word of Thanks

Unit of Tropical Laboratory Medicine, ITM
Partners of ITM in DR Congo, Burkina Faso, Benin, Mozambique and Cambodia
Alumni and students of ITM Tropical Medicine International Health
World Health Organization Prequalification Program
Roll Back Malaria Partnership
 Médecins sans Frontières Paris
EUCAST
Extra slides on the WHO PQ
Product dossier review

- Assessing evidence in support of *safety and performance* of the product;
- Assessing the product *design and manufacture*;
- Determining if the *manufacturer’s quality management system* is of an adequate standard to warrant an inspection of the manufacturing site.
Laboratory evaluation of the product

- To evaluate the performance and operational characteristics of the product
- Carried out by specified WHO Collaborating Centre(s) or designated laboratory(ies), against pre-determined performance criteria established by WHO.
- The manufacturer should send sufficient quantities (test kits and/or instruments) from at least two different lots
- If necessary, special equipment needed to perform the assay must be made available by the manufacturer at no charge
To assess compliance of quality management system and manufacturing practices
To verify the content of the product dossier

*Stage 1 inspection:* documentation related to quality management. A satisfactory stage 1 inspection is a pre-condition for stage 2

*Stage 2 inspection:* on-site comprehensive evaluation of the quality management system and production processes

All nonconformities will have to be addressed by the manufacturer through suitable corrective actions.

Re-inspection may occur to ensure ongoing compliance with prequalification requirements.

Re-inspections will typically occur every 3 to 5 years after prequalification, unless an earlier re-inspection is necessary
Post-market surveillance

To monitor the ongoing compliance of prequalified products with PQ requirements ("Post-Market Surveillance of IVD")

- The manufacturer will notify WHO of any post-market events that have/could have affected the performance of the assay, safety of the patients, users or any person associated with the product; and/or of any post-market events that require corrective actions.

- If required, it will supply sufficient quantities of the product to WHO or designated laboratories, for surveillance testing.

- Any post-market events/complaints concerning a prequalified product that is communicated to WHO will be investigated.

- WHO is entitled to make vigilance reports and product alerts public, and to share results/reports with the relevant NRAs and interested UN agencies or other intergovernmental organizations.