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

Cathy A. Petti,[1,2] Christopher R. Polage,[2] Thomas C. Quinn,[3,4] Allan R. Ronald,[5] and Merle A. Sande[1]

[1]Departments of Medicine and Pathology, University of Utah School of Medicine, and [2]ARUP Laboratories, Salt Lake City, Utah; [3]Department of Medicine, Johns Hopkins School of Medicine, Baltimore, and [4]Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland; and [5]Faculty of Medicine, University of Manitoba, Winnipeg, Canada

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?

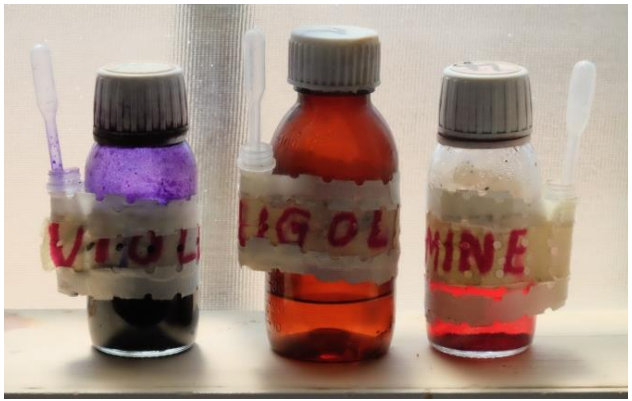
Reasons for poor laboratory performance:

- 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

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

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

Antimicrobial agent	Disk content (µg)	Range[1]	Bio-Rad	Lio-filchem	BD	Abtek	SirScan	Oxoid	HiMedia	Bio-analyse	Mast
Benzylpenicillin	1 unit	EUCAST			L		H		NA	H	
Amoxicillin-clavulanic acid	20-10	EUCAST/CLSI	H			L			H		
Piperacillin-tazobactam	30-6	EUCAST				L	H		NA		
Oxacillin	1	EUCAST		L	L		L		H	L	
Mecillinam	10	EUCAST/CLSI				L	H		H	H	
Cefotaxime[2]	5	EUCAST				NA			NA		
Cefoxitin[3]	30	EUCAST	H*	H		NA			L*		
Ceftazidime	10	EUCAST				L			L		
Meropenem[3]	10	EUCAST/CLSI	H	H*		L	H	H	H	H	H
Ciprofloxacin[3]	5	EUCAST/CLSI	L		L	L			H		L
Norfloxacin	10	EUCAST/CLSI				L	L		H*		
Pefloxacin	5	EUCAST		L	L	NA	NA		H		
Gentamicin	10	EUCAST/CLSI			H	L	NA		H		
Tobramycin	10	EUCAST/CLSI	NA	H					H*		
Erythromycin	15	EUCAST		L	L	L	L		H	L*	
Tetracycline	30	EUCAST		L	L*	L	L*			L	L

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

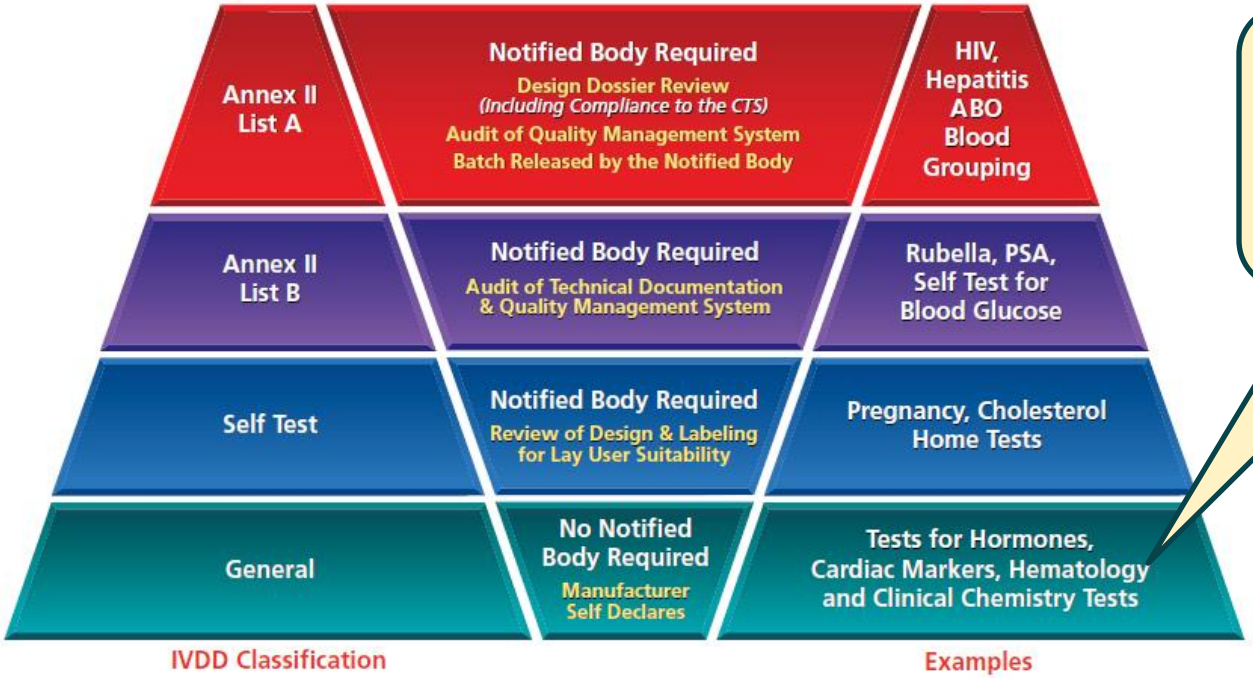
(International Medical Device Regulators Forum, www.imdrf.com)

TABLE 1: General classification of IVDD.

Class	Individual risk	Public health risk	Examples
A	•	•	
B	••	•	
C	•••	••	
D	•••	•••	

(•) Low, (••) moderate, and (•••) high.

CE mark is not always a guarantee for intrinsic quality



Self-declaration of conformity to CE requirements by manufacturer

Examples: Falsification

rare, small-scale, anecdotal (scale, profit margin)

HX895655

2014/02/20

1.09204.0502

500 ml

IMO: METHANOL SOLUTION
ICAO: METHANOL SOLUTION

IVD CE

C.I. 45380 2,4 g/l
C.I. 52015 + Azur 4,1 g/l
1 l = 0,99 kg

Lagern bei +15°C bis 25°C. Lösung stets frisch bereiten. Spezifikation auf Anfrage. Gebrauchsanweisung im Internet/auf Anfrage.

Store at +15°C to 25°C. Use only freshly prepared solution. Specification on request. Instructions for use on Internet/ on request.

Conserver de +15°C à +25°C. N'utiliser que des solutions préparées fraîchement. Spécification sur demande. Mode d'emploi sur Internet/sur demande.

Conservare tra +15°C e 25°C. Adoperare solo soluzioni preparate di fresco. Specifiche a richiesta. Istruzione per l'uso in Internet / su richiesta

Almacenar de +15°C hasta +25°C. Usar solamente soluciones recién preparadas. Especificación a solicitud. Instrucciones de uso en Internet/ a solicitud.

Leichtentzündlich
Highly flammable
Facilement inflammable
Facilmente inflammable
Fácilmente inflamable

Giftig
Toxic
Toxique
Tossico
Tóxico

Microscopy

Giemsas Azur-Eosin-Methylenblaulösung
für die Mikroskopie
(enthält Methanol)

Giemsa's azur eosin methylene blue solution
for microscopy
(contains methanol)

Azur-éosine-bleu de méthylène selon Giemsa en solution
pour la microscopie
(contient méthanol)

Giemsa soluzione azur-eosina-blu di metilene
per microscopia
(contiene Metanolo)

Azur-eosina-azul de metileno según Giemsa en solución
para microscopia
(contiene Metanol)

4 022536 111889

Merck KGaA
64271 Darmstadt, Germany
Tel. +49(0)6151 72-2440
www.merck.de

MERCK

R: 11-23/24/25-39/23/24/25 S: 7

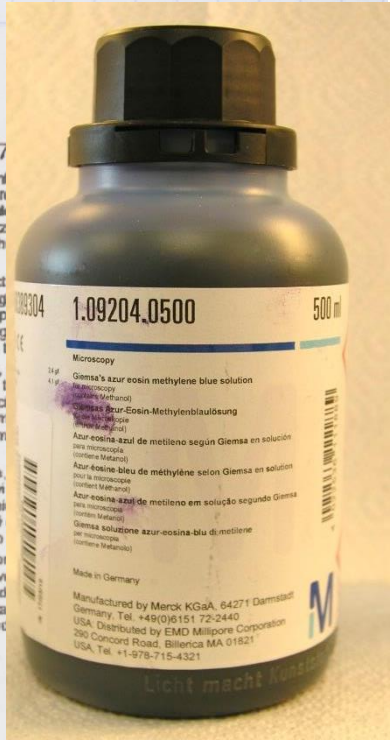
Leichtentzündlich. Giftig beim Einatmen, Verschl
Giftig: e ste Gefahr irreversiblen Schadens dur
und durch Verschlucken. * Behälter dicht geschl
- Nicht rauchen. Bei der Arbeit geeignete Schutz
Bei Unfall oder Unwohlsein sofort Arzt hinzuzieh
vorzeigen)

Highly flammable. Toxic by inhalation, in contact
danger of very serious irreversible effects throug
swallowed. * Keep container tightly closed. Keep
smoking. Wear suitable protective clothing and g
unwell, seek medical advice immediately (show t

Facilement inflammable. Toxique par inhalation,
ingestion. Toxique: danger d'effets irréversibles
avec la peau et par ingestion. * Conserver le réc
toute flamme ou source d'étincelles - Ne pas fum
des gants appropriés. En cas d'accident ou de m
médecin (si possible lui montrer l'étiquette).

Facilmente infiammabile. Tossico per inalazione,
Tossico: pericolo di effetti irreversibili molto grav
per ingestione. * Conservare il recipiente ben chi
sciante - Non fumare. Usare indumenti protettivi
malessere consultare immediatamente il medico

Fácilmente inflamable. Tóxico por inhalación, po
Tóxico: peligro de efectos irreversibles muy grav
ingestión. * Manténgase el recipiente bien cerrad
fuente de chispas - No fumar. Úsense indumenta
En caso de accidente o malestar, acúdase inmed
muéstesele la etiqueta).



Examples: Falsification

China has a lucrative market for fake research reagents.
Nature **2017;** 454: 148-150

THE SECRET WAR AGAINST COUNTERFEIT SCIENCE

CHINA HAS A LUCRATIVE MARKET FOR FAKE RESEARCH REAGENTS. NOW SOME SCIENTISTS ARE FIGHTING BACK.

BY DAVID CYRANOSKI

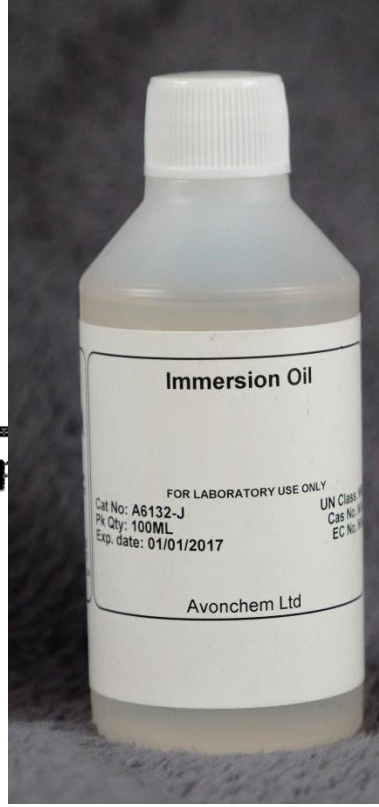
In 2013, Huang Song walked into a printing shop in northwestern Beijing and stumbled upon evidence of a brazen and widespread criminal enterprise. Huang was just 15 kilometres from Beijing's National Institute of Biological Sciences, where he does synthetic-biology research. Scouting out a small desktop machine to produce the hundreds of labels needed for his experiments, he asked if a certain model could print on heat-resistant paper. The shop owner proudly pulled out some samples he had made for customers using the same machine.

Huang was shocked to see names such as Abcam and Cell Signaling Technology on labels that looked exactly like those on vials of expensive antibodies produced by the Western companies. Although the writing meant nothing to the friendly shop owner, for Huang it directly contradicted what he and a number of his colleagues had long suspected: many of the antibodies sold by Chinese distributors were not what they were supposed to be. Counterfeiters were getting fake and diluted research reagents on to the market, and this shop in Zhongguancun, Beijing's premier technology park, was one of the places they were buying machines to make their labels. "I had a suspicion. That confirmed it," Huang says.

China is famous for knock-off DVDs, Louis Vuitton bags and Rolex watches. But counterfeit reagents aren't on sale in busy public markets. They are sold through sophisticated websites, mixed in with legitimate supplies, and sourced and sold using a network of unwitting partners, such as the Zhongguancun shopkeeper. Even university cleaning staff have been implicated in the hidden process that creates counterfeit laboratory products, including basic chemistry reagents, serum for cell culture and standard laboratory test kits. Although it's

- 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 ….

Falsification Immersion oil



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

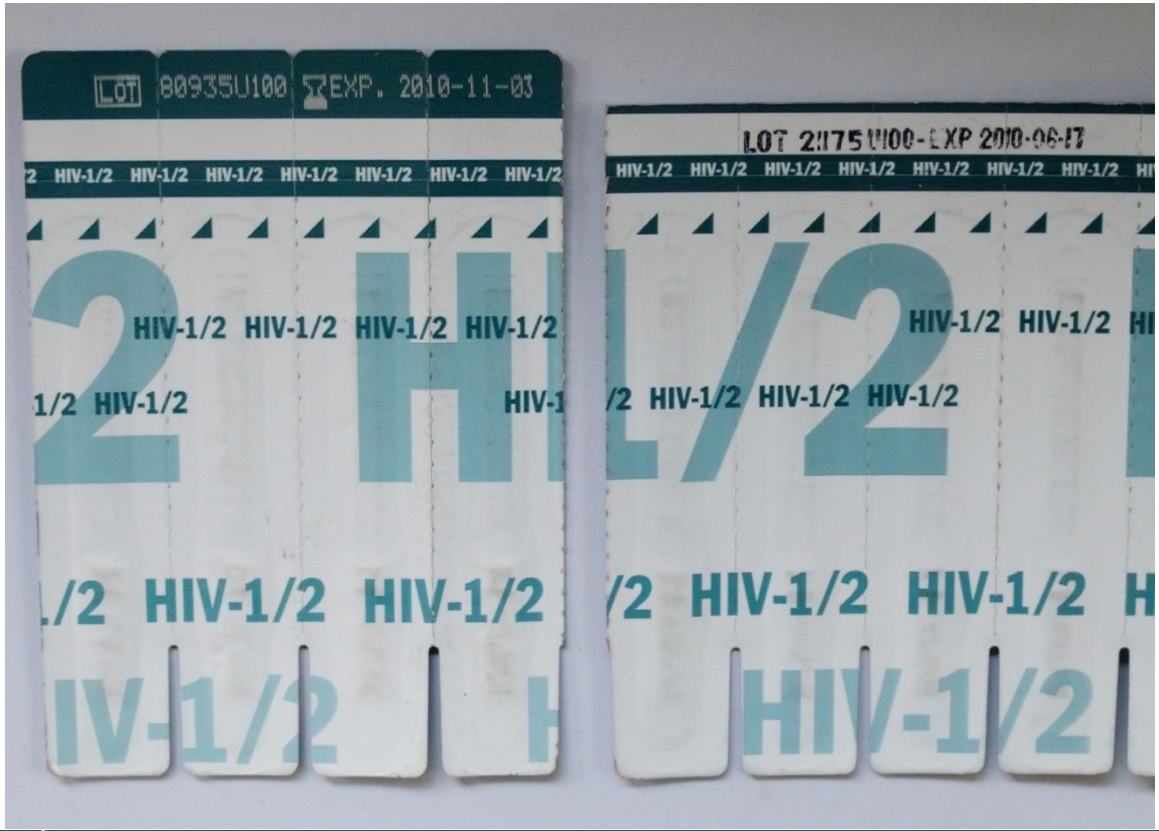
Référence	: FC055780
Date	: 03/06/14
Mode de règlement	: Comptant
Document libellé en	: Dollar US
A payer avant le	: 03/06/14
Compte	: 411CLEXC0
Code	: CLEXC

CLIENT EXCEPTIONNEL
KINSHASA
KINSHASA
KINSHASA
Congo

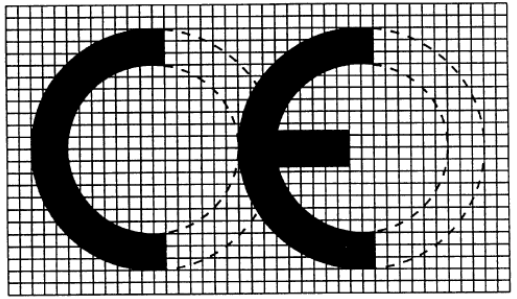
Référence	Désignation	Unité	Quantité	Prix Unitaire	% Rem.	Montant H.T.
	-Bon de livraison N° BL055456 du 03/06/2014					

Falsification

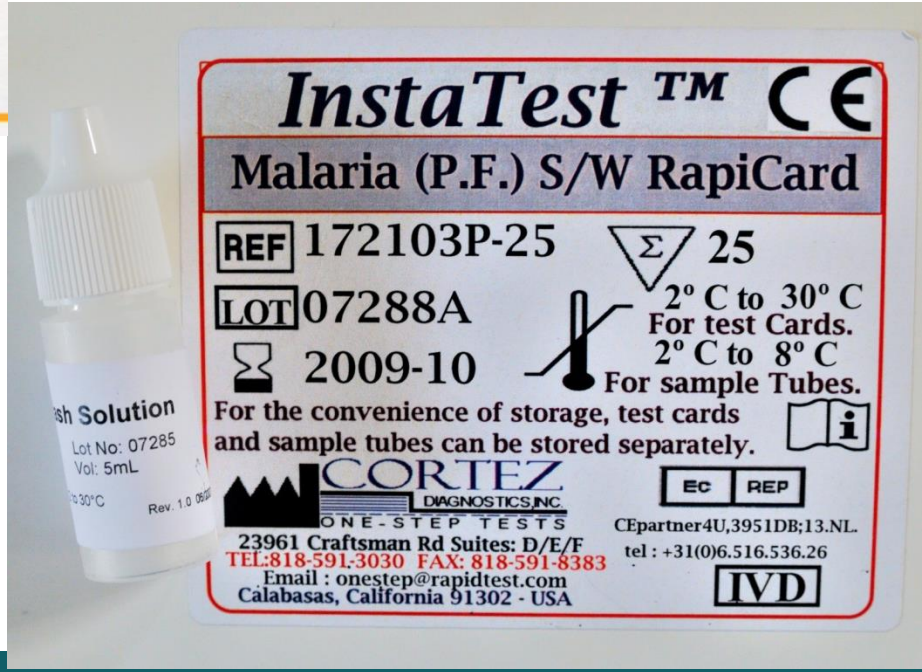
Tampering /of expiry date



Falsification – some hints about het CE mark



Symbol outlines
European Representative (address)



Hints about the CE mark

Substandards

common and large scale

Mukadi *et al. Malaria Journal* 2011, **10**:308
http://www.malariajournal.com/content/10/1/308

MALARIA JOURNAL

RESEARCH Open Access

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

Pierre Mukadi[1], Philippe Gillet[2*], Albert Lukuka[1,3], Ben Atua[3], Simelo Kahodi[4], Jean Lokombe[1,5], Jean-Jacques Muyembe[1,5] and Jan Jacobs[2,6]

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

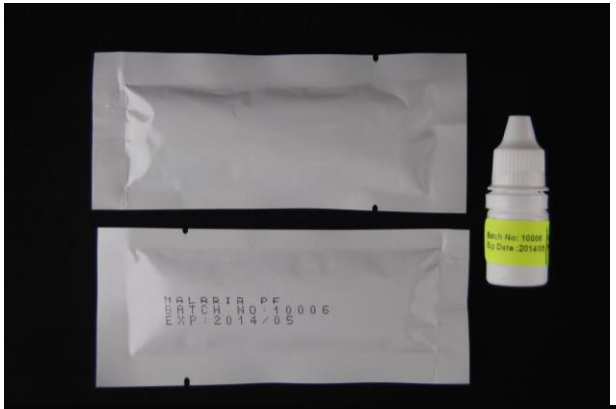
Note:

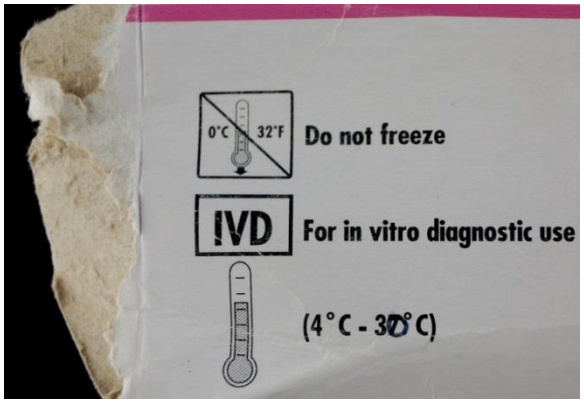
CE mark focuses on the European Community

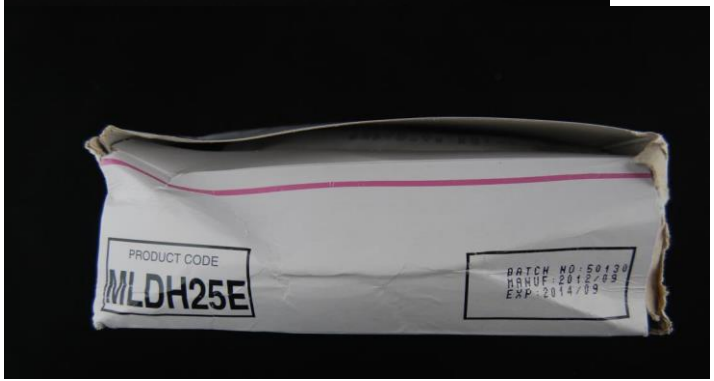
- Climate, infrastructure
- Population assessed
- End-user's level!
- Lab/Clinician's interphase

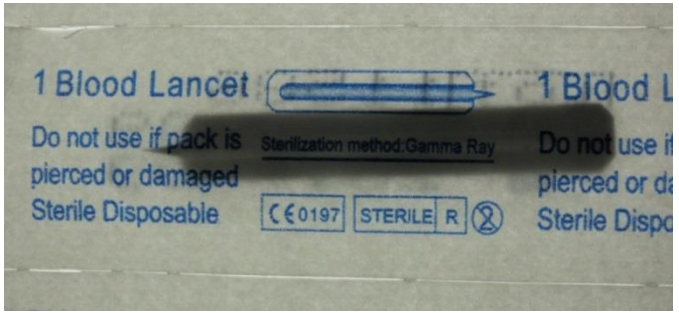
Substandards

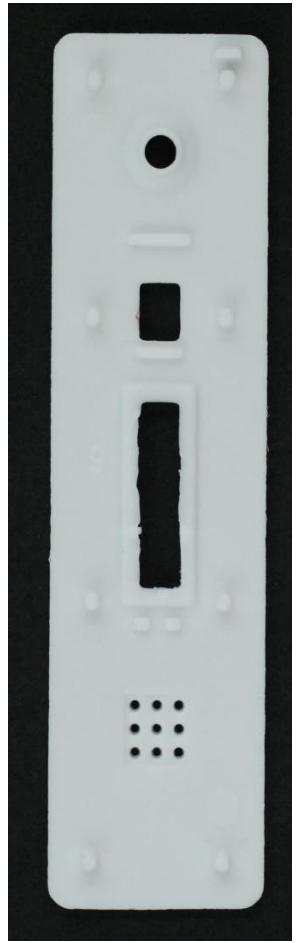
Pressure on price – volumes – lead times











Substandards

Pressure on price – volumes – lead times

Barbé *et al. Malaria Journal* 2012, **11**:326
http://www.malariajournal.com/content/11/1/326

MALARIA JOURNAL

RESEARCH Open Access

Assessment of desiccants and their instructions for use in rapid diagnostic tests

Barbara Barbé[1], Philippe Gillet[1], Greet Beelaert[2], Katrien Fransen[2] and Jan Jacobs[1*]

Procurement and Supply

Errors
Product codes too similar
No alert from the manufacturer

OPEN ACCESS Freely available online

PLOS ONE

External Quality Assessment of Reading and Interpretation of Malaria Rapid Diagnostic Tests among 1849 End-Users in the Democratic Republic of the Congo through Short Message Service (SMS)

Pierre Mukadi[1,2], Philippe Gillet[3], Albert Lukuka[1,4], Jacques Muyembe[1,7], Jozefien Buyze[3], Jan Jacobs[3],

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).

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pating in the EQA.
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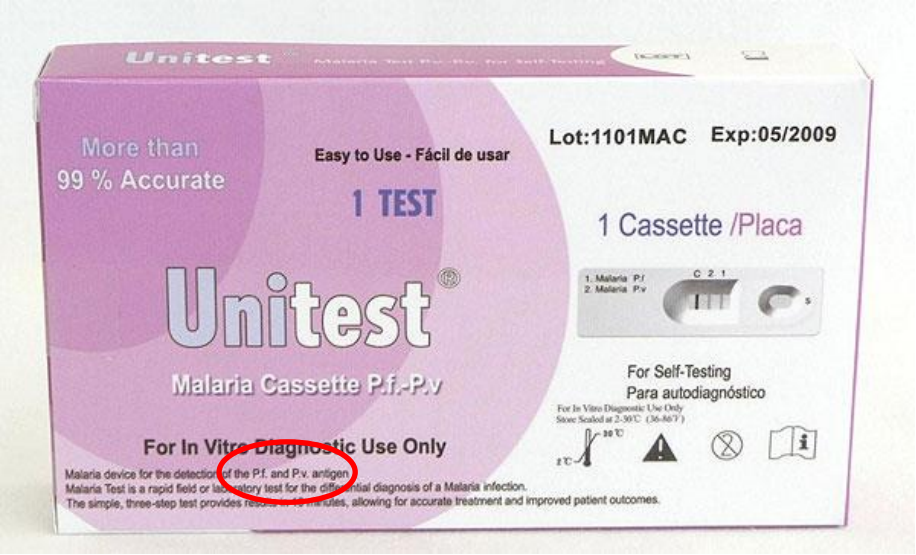
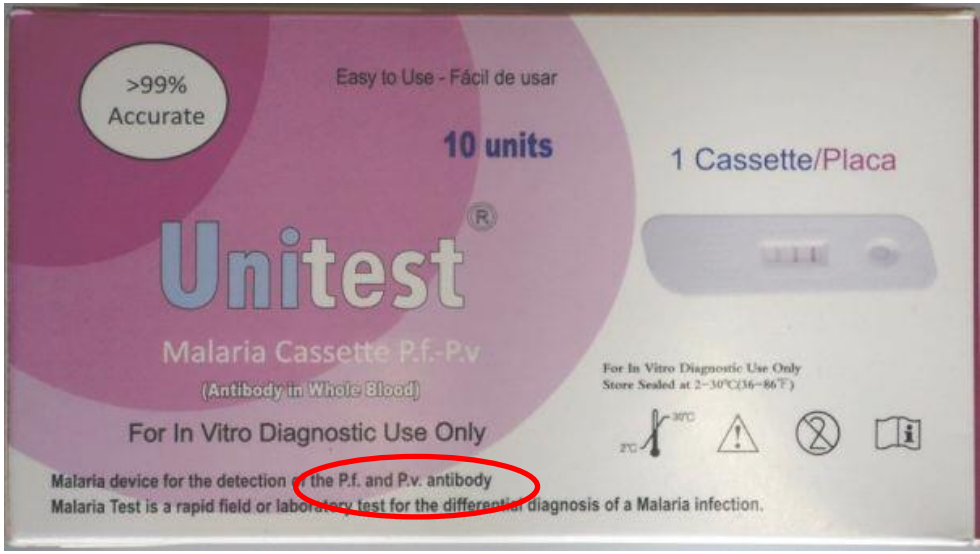
Procurement and supply What we ordered and what we received





Labeling is part of the IVD risk mitigation

Poor or wrong information instructions for use

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

One Step Malaria P.f / P.v Ab Test Device (WB/Serum/Plasma)

1. Explanation of the test

Malaria is a serious, sometimes fatal, parasitic disease characterized by fever, chills, and anemia and is caused by a parasite that is transmitted from one human to another by the bite of infected Anopheles mosquitoes. There are four kinds of malaria that can infect humans: Plasmodium falciparum, P. vivax, P. ovale, and P. malariae. In humans, the parasites (called sporozoites) migrate to the liver where they mature and release another form, the merozoites. The disease is a major health problem in much of the tropics and subtropics. More than 200 million people in the world have malaria.

At the present, malaria is diagnosed by looking for the parasites in a drop of blood. Blood will be put onto a microscope slide and stained so that the parasites will be visible under a microscope. At the most recent, clinical diagnostic issues related to malaria are the detection of malaria antibodies in human blood by immunoassay. The ELISA format and immunochromatographic format (rapid) to detect antibody of malaria are available recently.

The Malaria P.f/P.v Ab test is a immunochromatographic (rapid) test for the qualitative detection of antibodies of all isotypes (IgG, IgM, IgA) specific to Plasmodium falciparum and Plasmodium vivax simultaneously in human serum or plasma or whole blood . The Malaria P.f/P.v test contains a membrane strip, which is pre-coated with

4) Sterile lancet
5) Pipette

A compelet set for home use may also contain the folloeing accessories in a separate poly bag:
1) Pipette
2) Alcohol pad
3) Bandage

3. Precautions

The Malaria P.f/P.v Ab test devices should be stored at room temperature. The test device is sensitive to humidity and as well as to heat. Perform the test immediately after removing the test device from the foil pouch. Do not use it beyond the expiration.

4. Specimen collection and storage

1) Fingerstick Specimens (Whole Blood)
Clean the area to be lanced with Alcohol prep pad. Squeeze the end of the fingertip and pierce it with the sterile lancet.
Wipe away the first drop of blood with sterile gauze or cotton. Using Disposable pipette, collect blood from the puncture site.
2) (Serum or plasma) Centrifuge whole blood to get plasma or serum specimen.
3) If serum is not tested immediately, it should be refrigerated at 2-8°C. For storage periods greater than three days, freezing is recommended. They should be brought to room temperature prior to use.
4) Serum containing precipitate may yield inconsistent test results . Such specimens must be clarified prior to assaying

Poor or wrong information in instructions for use

Promise versus Reality: Optimism Bias in Package Inserts for Tuberculosis Diagnostics

Claudia M. Denkinger,[a] Jasmine Grenier,[b] Jessica Minion,[c] and Madhukar Pai[d,e]

Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA[a]; Faculty of Medicine, McGill University, Montreal, Quebec, Canada[b]; Department of Medical Microbiology & Immunology, University of Alberta, Edmonton, Alberta, Canada[c]; Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada[d]; and Respiratory Epidemiology & Clinical Research Unit, Montreal Chest Institute, Montreal, Quebec, Canada[e]

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.

No information (labeling including instructions for use)

Retrospective evaluation of immunochromatographic *Salmonella* diagnostic tests for the rapid detection of *Salmonella* serovars in blood culture fluid

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

INSTITUTE OF TROPICAL MEDICINE ANTWERP

(Serum/Stool)

Sensitivity:

[redacted] 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

1. Ivanoff BN, Levine MM, Lambert PH. Vaccination against typhoid fever: present status. Bulletin of the World Health Organization 1994; 72: 957-71.
2. Gotuzzo E, Frisancho O, Sanchez J, Liendo G, Carillo C, Black RE, Morris JG. Association between the acquired immunodeficiency syndrome and infection with Salmonella typhi or Salmonella paratyphi in an endemic typhoid area. Archives of Internal Medicine 1991; 151: 381-2.

Poor or wrong information
Lack of Harmonization

Hidden errors, brand names and types

Add 19 g to 1 litre of distilled water to which 4 g of Sodium Biselenite (Oxoid L121) has been added. Warm to dissolve. Mix well and fill into containers to a depth of 5 cm. Sterilize in a boiling water bath, or in free flowing steam, for 10 minutes. DO NOT AUTOCLAVE.

B1111/13

Añadir 19 g a 1 litro de agua destilada a la cual se ha añadido 4 g de biselenito sódico (Oxoid L 121). Calentar hasta disolución, mezclar y distribuir en tubos hasta una altura de 5 cm. Esterilizar en baño de agua hirviente o en autoclave a vapor fluente, durante 10 minutos. NO AUTOCLAVAR.

4 g Natriumbiselenit (Art.-Nr. L 121) in 1 l Aqua dest. lösen

One product is lacking
Sodium Biselinite
= the selective component!

Xn

R20/22, 33, 37, 59, 20/21, 28, 36.

Harmful

Bouillon séléniteux

Base servant de milieu d'enrichissement pour l'isolement de *Salmonella*

Mode d'emploi : Mettre 23 g de poudre en suspension dans 1 L d'eau purifiée. Chauffer jusqu'à ébullition. Ne pas surchauffer. NE PAS AUTOCLAVER. Pour contrôler les performances du produit, tester des échantillons du produit fini en utilisant des cultures de contrôle stables, typiques.

Formule approximative* par litre

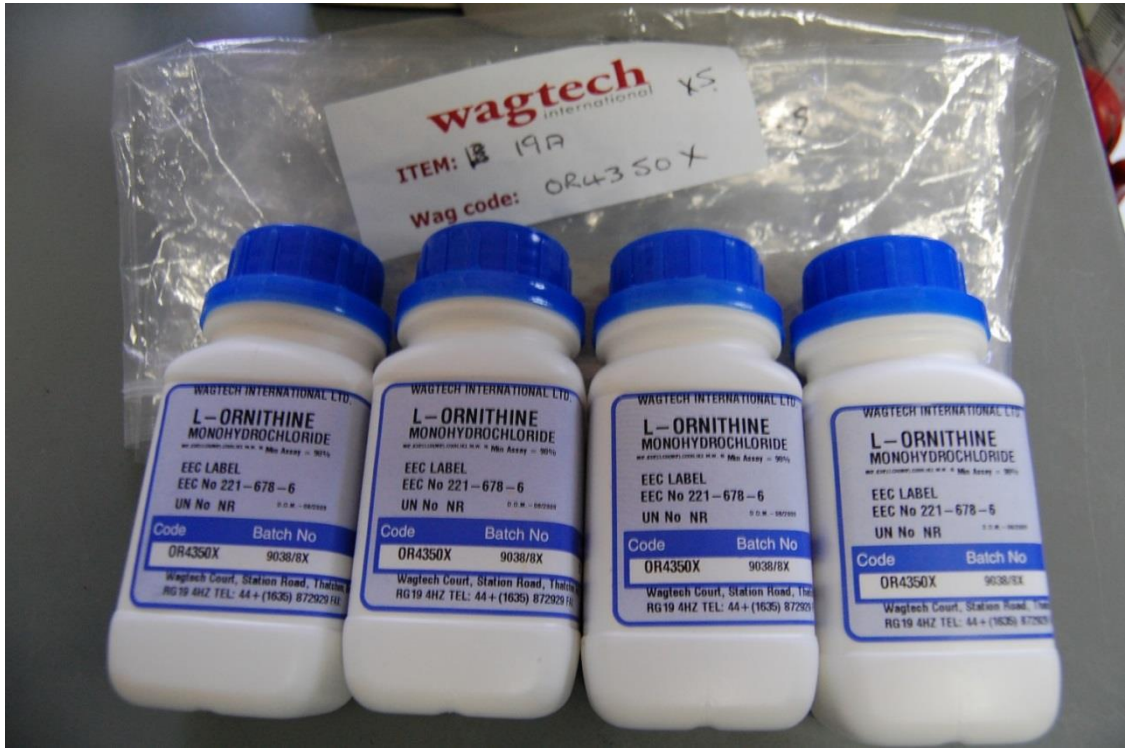
Digestion pancréatique de caséine ..... 5,0 g
Lactose ..... 4,0 g
Sélénite de sodium ..... 4,0 g
Phosphate de sodium ..... 10,0 g

* Ajustée et/ou complémentée en fonction des critères de performances imposés.

Pour usage en laboratoire • pH final 7,0 ± 0,2

Produit hygroscopique • Bien boucher le récipient.

Too Expensive



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)

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℃) before te sting.
- Place the test card on a clean and level surface.

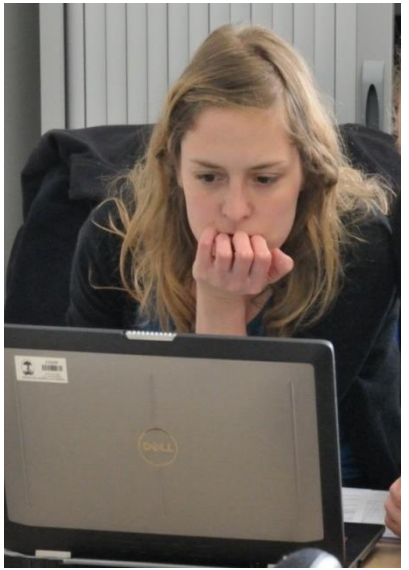
Test Procedure for Serum and Plasma Specimen:

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 Barbé[1✉], Kristien Verdonck[1✉*], Sayda El-Safi[2], Basudha Khanal[3], Syna Teav[4], Jean-Roger Lilo Kalo[5], Raffaella Ravinetto[1,6], François Chappuis[7], Marleen Boelaert[1], Jan Jacobs[1,8]

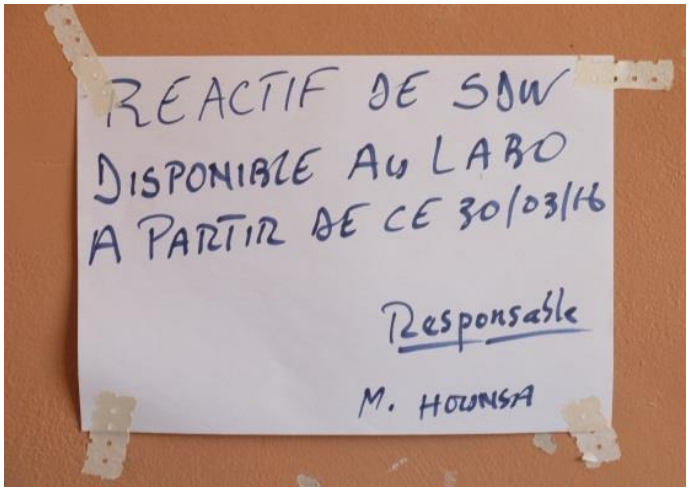


Dear Barbara,
We did have validation done on the change.
As I mentioned the in-house validation is usually limited and full evaluation would be required at customers end.
If you are not comfortable with the new reading time simply disregard the new version of the package insert"

Diagnostic Stewardship

The right IVD for the right indication

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



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journal homepage: http://www.elsevier.com/locate/trstmh

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

Octavie Lunguya[a,b], Marie-France Phoba[a,b], Steve Ahuka Mundeke[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 laboraties

Note: External Quality Assessment – support from the North

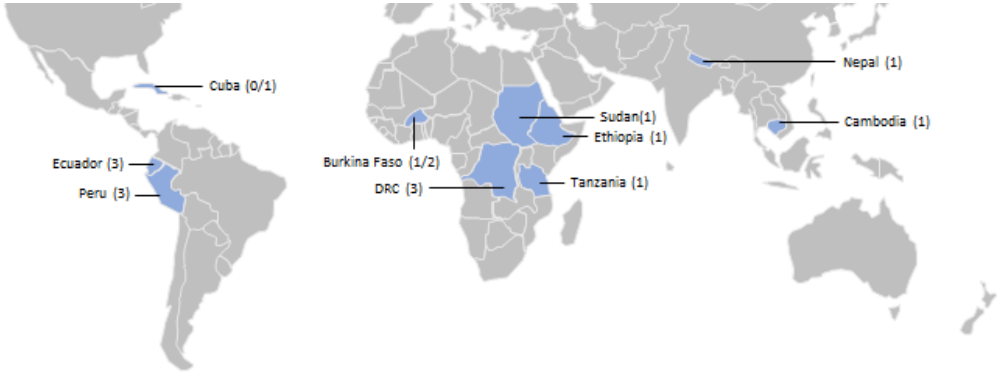
Diagnostic bacteriology in low and middle income countries

EXTERNAL QUALITY ASSESSMENT OF IDENTIFICATION AND ANTIBIOTIC SUSCEPTIBILITY TESTING

Barbara Barbé [1], Sien Ombelet [1], Philippe Deffranne [2], Kris Vernelen [2], Jan Jacobs [1,3]

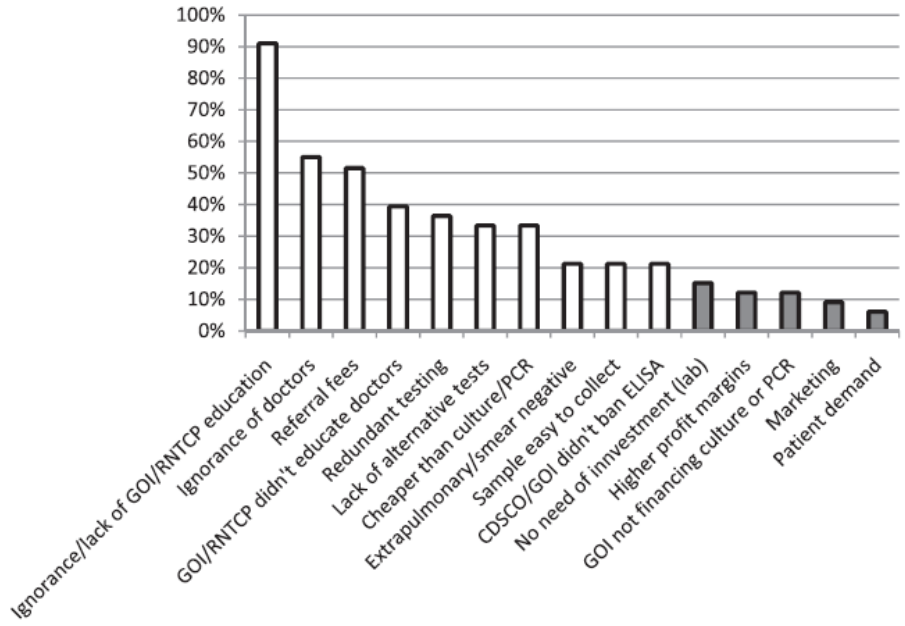
[1]Institute of Tropical Medicine, Antwerp, Belgium [2]Quality of Medical laboratories, Institute of Public Health, Brussels, Belgium [3]Department of Microbiology and Immunology, KU Leuven, Belgium

INSTITUTE OF TROPICAL MEDICINE ANTWERP



- For-free use of validated EQA pannels 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 Jarosławski [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

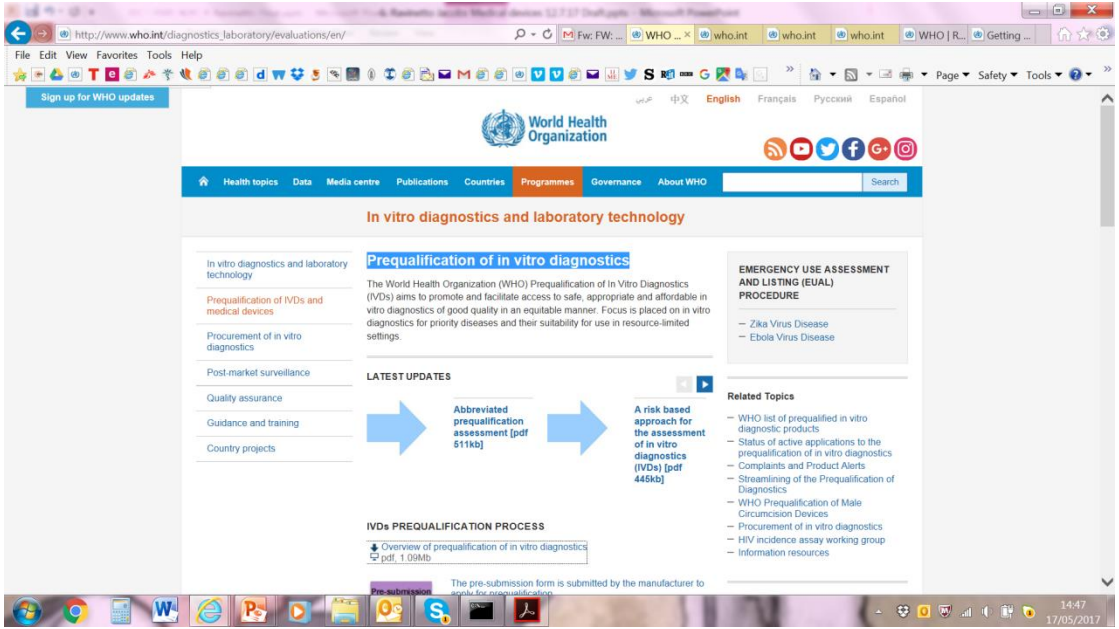
referral fees (incentives) which encourage the use of serodiagnostics. Doctors who request serological tests are often offered by the private laboratories about 20–50% of the price (i.e., between 150 and 300 rupees) paid by the patient.

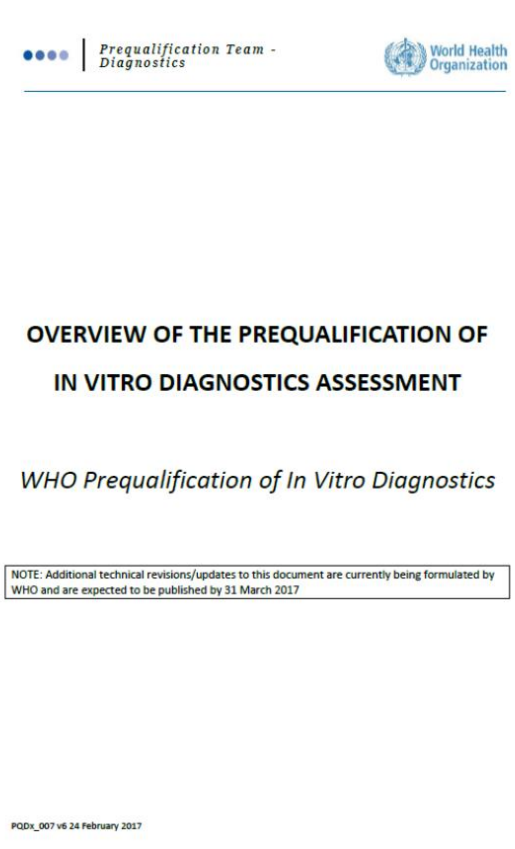
Take-home messages about quality of IVD in low resource settings

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

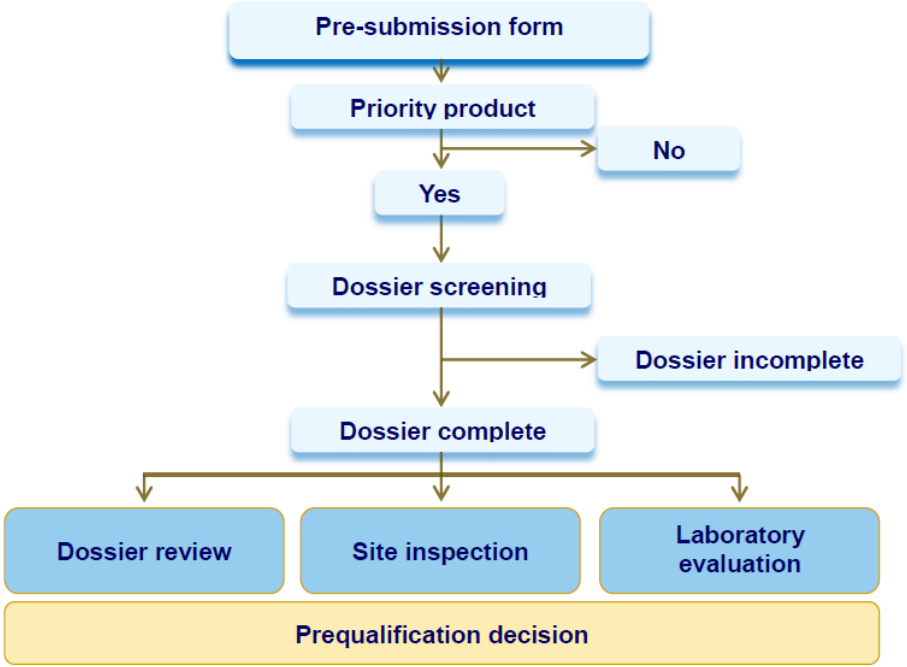


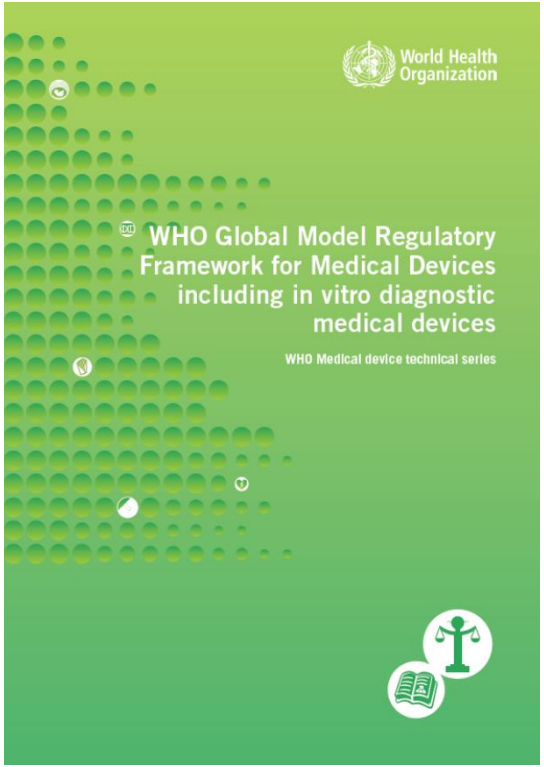
Figure 1 Prequalification of diagnostics: full assessment process

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

Manufacturing site inspection

- 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.