IMPACT OF REGULATORY REQUIREMENTS: NAT SCREENING

The WHO PQ Programme and its Updated Role after the Outbreaks of Ebola and Zika Virus

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World Health Organization

Aim of WHO Prequalification: Diagnostics Assessment

To promote and facilitate access to safe & appropriate IVDs of good quality in an equitable manner

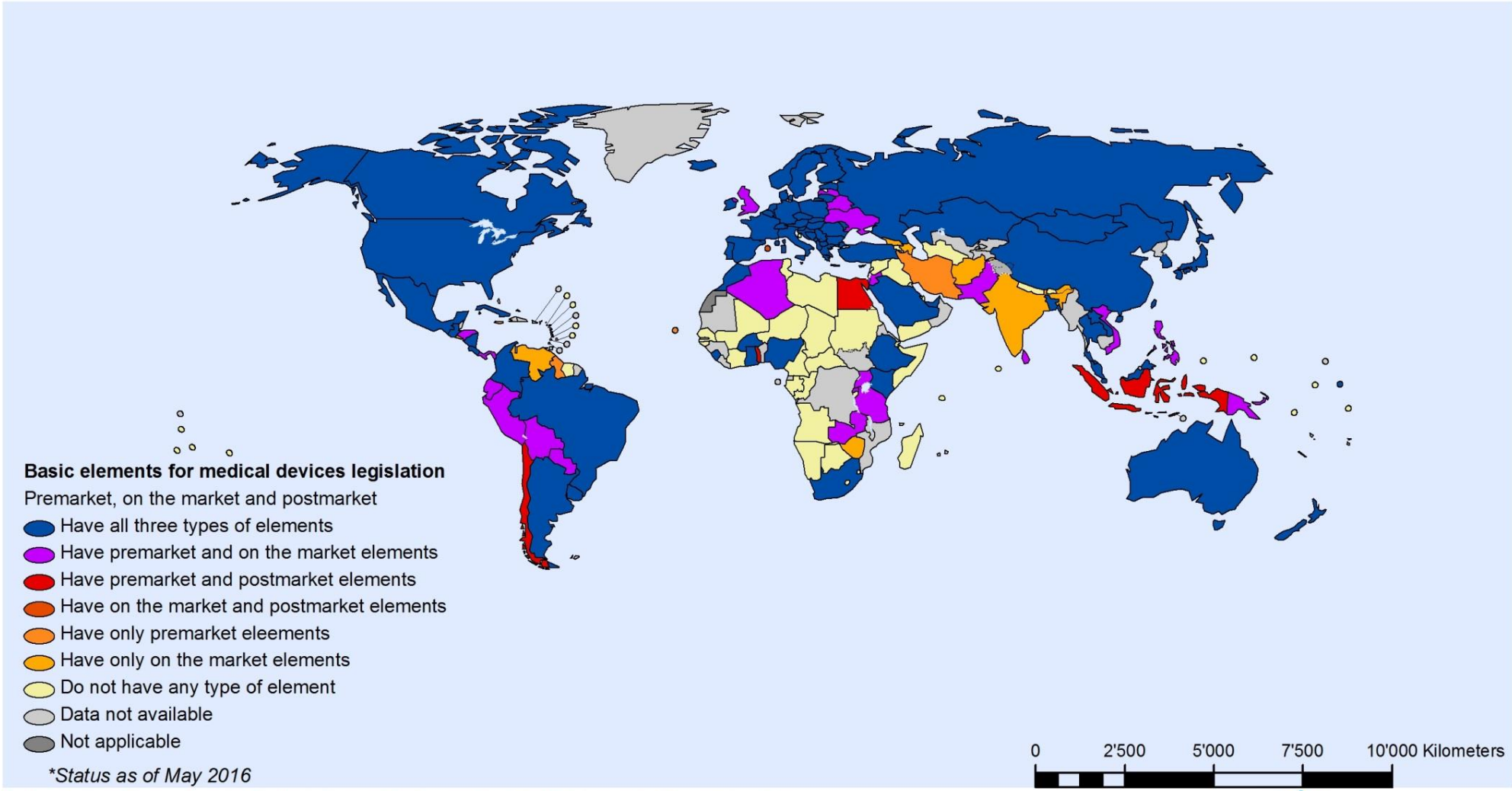
Customers

- WHO Member States
- UN agencies
- Funding agencies
- Procurement agencies

IVDs

- HIV
- Malaria
- HCV
- HBV
- CD4
- HPV
- G6PD

*Basic elements for medical devices legislation. Premarket, on the market and postmarket.



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Data Source: WHO Regulatory Status desk survey
May 2016 update
Map Production: Department of Essential Medicines and Health Products
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WHO Prequalification: IVDs

- Based on best regulatory practice
- Comprehensive assessment of safety, quality, performance and suitability for use in WHO member states
  - Dossier assessment
  - QMS assessment and inspection of manufacturing
  - Performance evaluation
- As with similar assessments by stringent regulatory bodies, this process can take between 6 months to over a year (depends usually on ability of the manufacturer)

Evolution of a new role for WHO PQ

- 2014 Ebola virus crisis highlighted the need for an emergency assessment procedure for vaccines, medicines and IVDs

- The procedure would need to be different from PQ in four major ways
  - Faster assessment process
  - Decision based on minimal evidence of safety and performance, given that few products would be at a mature stage in the development cycle
  - Rolling submissions acceptable as more data (evidence) is collected by the manufacturer
  - Need to be flexible

The evolution of a new role for the PQ Programme

- WHO PQ already had experience with other assessment mechanisms
  - Lab evaluation only
  - Expert Review Panel for innovative products
    - QMS and limited dossier

The evolution of a new role for the PQ Programme

- **Emergency Use Assessment and Listing (EUAL)** Procedure
  - To apply when there is a Public Health Emergency of International Concern (PHEIC)
  - A procedure that can be adapted to the circumstances of the emergency
  - Based on good regulatory practice

Emergency Use Assessment and Listing

- The Listing provides guidance including product-specific technical information to
  - UN procurement agencies,
  - WHO product utilization advisory committees,
  - national regulatory authorities (NRAs),
  - and others involved in efforts to control an epidemic.

The EUAL Procedure

- Where possible, the EUAL for IVDs procedure consists of:
  - A review of any existing documentary evidence of safety and performance
  - A desktop review of selected manufacturing and QMS documentation
  - A limited laboratory evaluation of relevant performance and operational characteristics of the product
- Possibility to abbreviate any of the steps if evidence of sufficient scrutiny by a stringent regulatory authority

EUAL: The Ebola Experience

- Few manufacturers had started to develop NAT and antigen detection assays
- Most had very little technical documentation
- Some had rudimentary QMS (ISO 13485) but not manufacturing capacity
- Clinical blood samples were not available for validation
  - restriction in transportation of clinical samples outside W Africa
- Testing required BSL-4 laboratories
- Therefore the manufacturers had minimal analytical and clinical performance data

Ebola EUAL and International Collaboration

- International support in the provision of EVD IVD expertise for Dossier and QMS review
  - Dossier requirements and review
  - Adoption of US FDA requirements for dossier (provided alignment and harmonised approach)
  - USA, Belgium, Australia, Switzerland
- International Support for WHO coordinated Lab and Field evaluations
  - BSL4 lab and LOD studies (Bernhard Nocht Institute, Germany)
  - Sierra Leone clinical performance study (Nigerian and PHE Labs and MoH SL)


By Guest Blogger - Feb 26, 2015

Testing The Test – A Scientist's Journey In Search Of A Rapid Ebola Diagnostic

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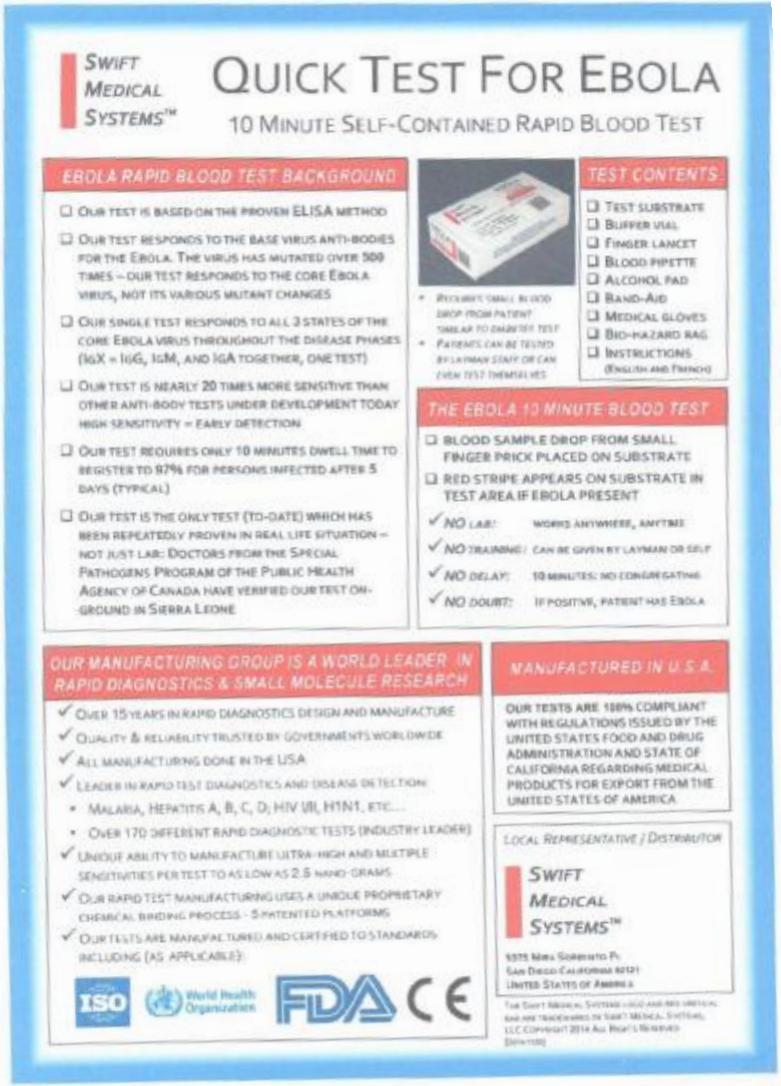
Ending the Ebola epidemic depends on a number of elements and quick diagnosis is a critical piece of the puzzle. Last week, the World Health Organization announced that the first rapid diagnostic test for Ebola will soon be available for use by the three most affected countries and their partners on the ground. This test is a significant breakthrough in the diagnosis of the Ebola virus. Resembling a take-home pregnancy kit, the test provides results in 15 minutes.

» Read More

EBOLA

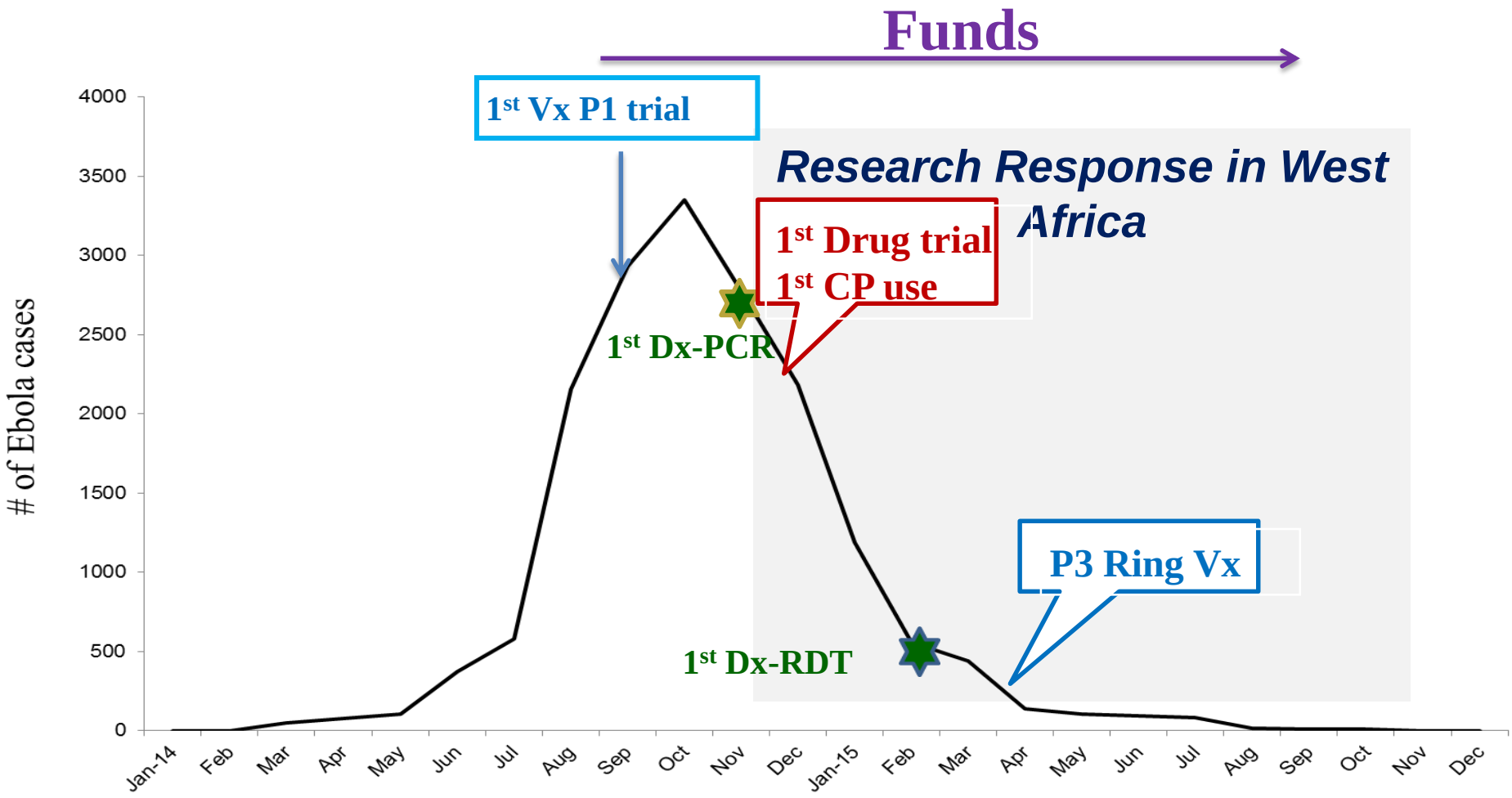
Ebola EUAL : Making a Difference

- WHO first listed a PCR, followed by a rapid antigen assay
- PCRs were able to be used in the internationally supported mobile laboratories
- Use of RDTs has proven sustainable



World Health Organization

WHO Research Response EBOLA



Response to the Ebola outbreak

World Health Organization

Photo: PAHO/Harald Ruiz

EUAL and the Zika Virus Experience

- Lessons learnt
  - Optimise international cooperation
  - Agree and publish requirements
  - Ensure requirements aligned
  - Abbreviate process where possible
  - Alignment /cooperation with other WHO/PAHO led initiatives
    - Input into testing strategies
    - WHO reference materials
    - TPP development

Zika Virus EUAL submission requirements

Instructions for Submission Requirements:

In vitro diagnostics (IVDs) Detecting Zika Virus Nucleic Acid or Antigen

Emergency Use Assessment and Listing of IVDs

Table 2: Organisms to be tested as well as analyzed in silico (for assays detecting Zika Virus) in specimens of intended use

Disease/Infectious agent		% Cross-reactivity	Laboratory testing	In silico analysis
Flavivirus	Dengue virus 1, 2, 3 and 4		✓	✓
	Yellow fever (optional)		✓	✓
	Yellow fever vaccine strain		✓	✓
	West Nile virus		✓	✓
Chikungunya			✓	✓
Parvovirus (B19)			✓	✓
Plasmodium falciparum			✓	✓
Flaviviruses	St. Louis encephalitis virus		×	✓
	Rocio virus		×	✓
	Ilheus virus		×	✓
	Iguape virus		×	✓
	Tick-borne encephalitis virus		×	✓
	Japanese encephalitis virus		×	✓
	Spondweni virus		×	✓
	Hepatitis C virus		×	✓
Alphaviruses	(Sindbis virus, Tonate virus and Una virus)		×	✓
	O'nyong-nyong virus		×	✓
	Barmah Forest virus		×	✓
	Ross River virus		×	✓
	Western Equine Encephalitis virus (WEE)		×	✓
	Eastern Equine Encephalitis virus (EEE)		×	✓
	Mayaro Virus		×	✓
Measles virus			×	✓
Rubella virus			×	✓
Adenovirus: all serotypes			×	✓
Hepatitis B virus			×	✓
HIV			×	✓

Current Status

- 2 RT-PCR IVDs listed
  - RT-PCR RealStar Zika Virus RT PCR Kit 1.0
  - Multiplex AccuPower®ZIKV (DENV, CHIKV) Multiplex Real-Time RT-PCR Kit
- Pipeline
  - 1 immunofluorescent assay
  - 3 RT-PCRs
  - 3 Rapid tests
  - 8 EIAs
- No new applications being accepted
  - Probability requirement will revert to full PQ

Overall EUAL experience: lessons learnt

- For most PHEIC diseases, few IVDs already exist. Rapid development of quality IVDs difficult
  - Reference standard/benchmark assay
  - Biobanks and access to panels and laboratories
  - Informed consent for use of left over specimens and country rights
  - General support to manufacturers R+D activities
  - Ethics approval
- Listing validity and next steps (PQ may not be possible)
- International cooperation vital
- Sustainability
- The mandate and need for WHO to undertake such a procedure is clear


Thank you