

IMPACT OF REGULATORY REQUIREMENTS: NAT SCREENING

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

Robyn Meurant

Dept of Essential Medicines and Health Products

Prequalification Team – Diagnostics Assessment



**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

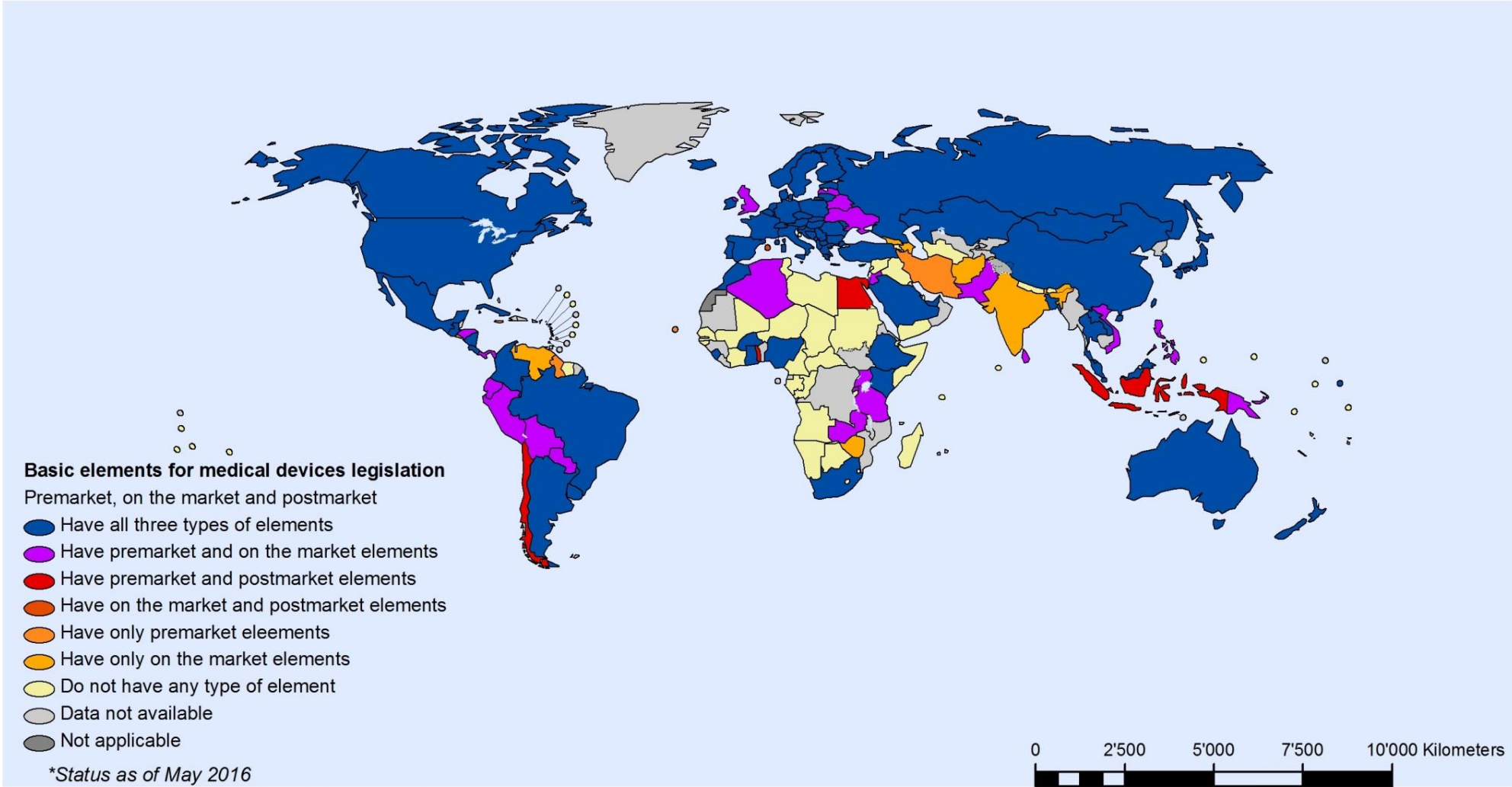
WHO Member States
UN agencies
Funding agencies
Procurement agencies

IVDs

HIV
Malaria
HCV
HBV
CD4
HPV
G6PD

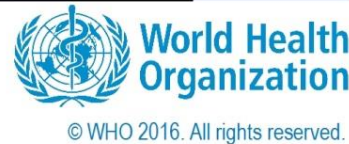


***Basic elements for medical devices legislation.
Premarket, on the market and postmarket.**



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

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



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

SWIFT MEDICAL SYSTEMS™ **QUICK TEST FOR EBOLA**
10 MINUTE SELF-CONTAINED RAPID BLOOD TEST

EBOLA RAPID BLOOD TEST BACKGROUND

- ❑ OUR TEST IS BASED ON THE PROVEN ELISA METHOD
- ❑ OUR TEST RESPONDS TO THE BASE VIRUS ANTI-BODIES FOR THE EBOLA. THE VIRUS HAS MUTATED OVER 500 TIMES – OUR TEST RESPONDS TO THE CORE EBOLA VIRUS, NOT ITS VARIOUS MUTANT CHANGES
- ❑ OUR SINGLE TEST RESPONDS TO ALL 3 STATES OF THE CORE EBOLA VIRUS THROUGHOUT THE DISEASE PHASES (IgX = IgG, IgM, AND IgA TOGETHER, ONE TEST)
- ❑ OUR TEST IS NEARLY 20 TIMES MORE SENSITIVE THAN OTHER ANTI-BODY TESTS UNDER DEVELOPMENT TODAY – HIGH SENSITIVITY = EARLY DETECTION
- ❑ OUR TEST REQUIRES ONLY 10 MINUTES DWELL TIME TO REGISTER TO 97% FOR PERSONS INFECTED AFTER 5 DAYS (TYPICAL)
- ❑ OUR TEST IS THE ONLY TEST (TO-DATE) WHICH HAS BEEN REPEATEDLY PROVEN IN REAL LIFE SITUATION – NOT JUST LAB: DOCTORS FROM THE SPECIAL PATHOGENS PROGRAM OF THE PUBLIC HEALTH AGENCY OF CANADA HAVE VERIFIED OUR TEST ON-GROUND IN SIERRA LEONE

TEST CONTENTS

- ❑ TEST SUBSTRATE
- ❑ BUFFER VIAL
- ❑ FINGER LANCET
- ❑ BLOOD PIPETTE
- ❑ ALCOHOL PAD
- ❑ BAND-AID
- ❑ MEDICAL GLOVES
- ❑ BIO-HAZARD BAG
- ❑ INSTRUCTIONS (ENGLISH AND FRENCH)

THE EBOLA 10 MINUTE BLOOD TEST

- ❑ BLOOD SAMPLE DROP FROM SMALL FINGER PRICK PLACED ON SUBSTRATE
- ❑ RED STRIPE APPEARS ON SUBSTRATE IN TEST AREA IF EBOLA PRESENT

✓ **NO LAB:** WORKS ANYWHERE, ANYTIME
✓ **NO TRAINING:** CAN BE GIVEN BY LAYMAN OR NLP
✓ **NO DELAY:** 10 MINUTES, NO CONGREGATING
✓ **NO DOUBT:** IF POSITIVE, PATIENT HAS EBOLA

OUR MANUFACTURING GROUP IS A WORLD LEADER IN RAPID DIAGNOSTICS & SMALL MOLECULE RESEARCH

- ✓ OVER 15 YEARS IN RAPID DIAGNOSTICS DESIGN AND MANUFACTURE
- ✓ QUALITY & RELIABILITY TRUSTED BY GOVERNMENTS WORLDWIDE
- ✓ ALL MANUFACTURING DONE IN THE USA
- ✓ LEADER IN RAPID TEST DIAGNOSTICS AND DISEASE DETECTION
 - MALARIA, HEPATITIS A, B, C, D, HIV, HB, HTN1, ETC...
 - OVER 170 DIFFERENT RAPID DIAGNOSTIC TESTS (INDUSTRY LEADER)
- ✓ UNIQUE ABILITY TO MANUFACTURE ULTRA-HIGH AND MULTIPLE SENSITIVITIES PER TEST TO AS LOW AS 2.5 NANO-GRAMS
- ✓ OUR RAPID TEST MANUFACTURING USES A UNIQUE PROPRIETARY CHEMICAL BINDING PROCESS - 5 PATENTED PLATFORMS
- ✓ OUR TESTS ARE MANUFACTURED AND CERTIFIED TO STANDARDS, INCLUDING (AS APPLICABLE):

MANUFACTURED IN U.S.A.

OUR TESTS ARE 100% COMPLIANT WITH REGULATIONS ISSUED BY THE UNITED STATES FOOD AND DRUG ADMINISTRATION AND STATE OF CALIFORNIA REGARDING MEDICAL PRODUCTS FOR EXPORT FROM THE UNITED STATES OF AMERICA

LOCAL REPRESENTATIVE / DISTRIBUTOR

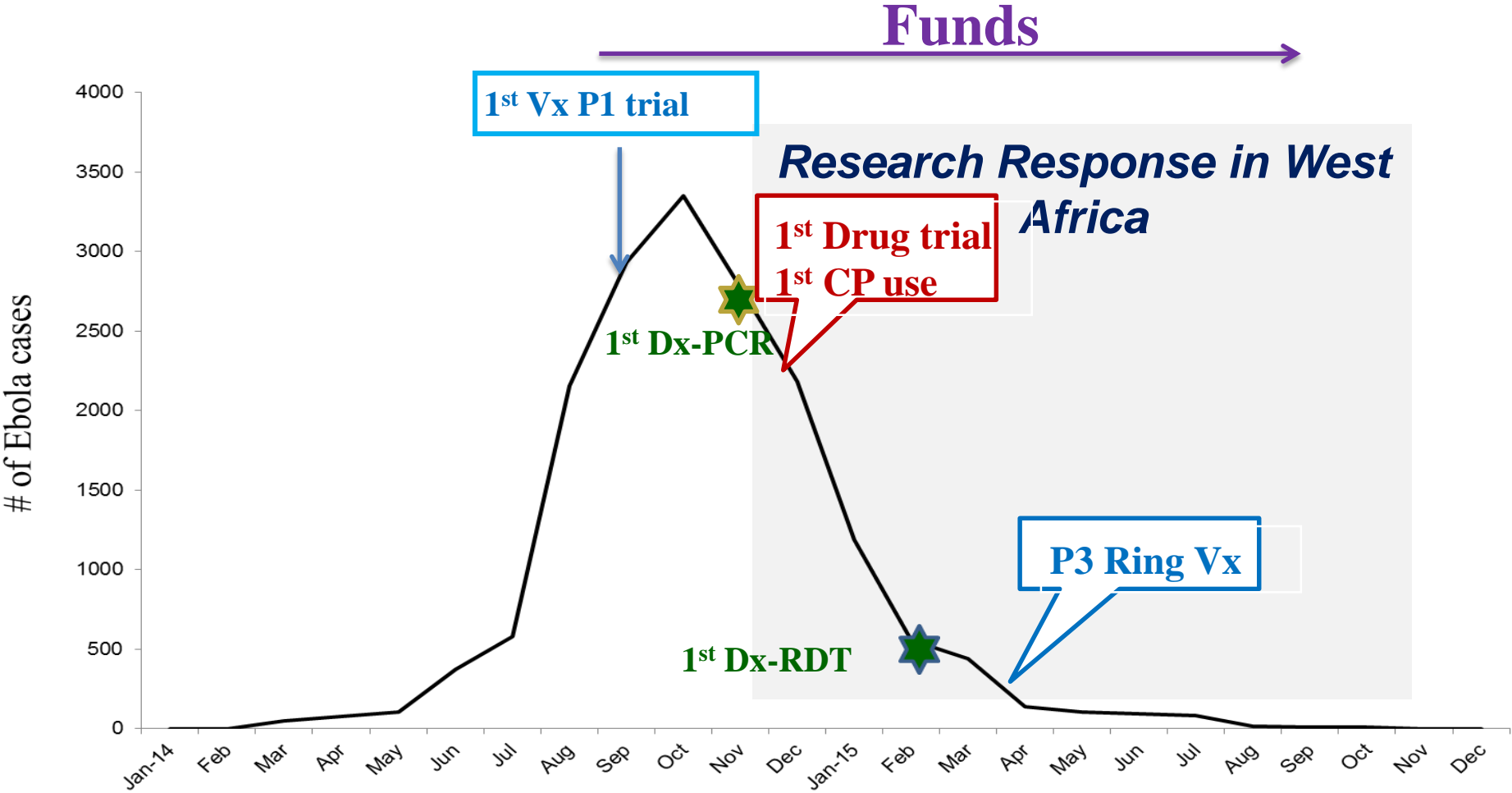
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1575 Mesa Solerito Pl.
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ISO World Health Organization FDA CE

WHO Research Response EBOLA



Response to the Ebola outbreak



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)			✓	✓
<i>Plasmodium falciparum</i>			✓	✓
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