WHO Emergency Use Assessment and Listing

R Meurant
On behalf of the
WHO PQ Team – Diagnostics Assessment
Emergency Use Assessment and Listing (EUAL)

Special procedure for assessment of health products in a public health emergency

2014 Ebola crisis highlighted the need for an emergency assessment procedure

It was recognised that the procedure would be different to prequalification

- Decision to list based on minimal evidence of safety and efficacy/performance
  - as few products at a mature stage in the product lifecycle
  - Based on immediate need
EUAL

A rapid, time-limited procedure for the assessment of quality, safety and efficacy/performance during an outbreak, based on a minimal level of information, was established for vaccines, medicines and IVDs and published in July 2015.

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

The disease has been declared by the WHO Director General to be a Public Health Emergency of International Concern (PHEIC)

WHO agrees that, based on the contingencies of the specific health emergency, it is reasonable to consider the product for assessment in the following circumstances:

- There are no products that have undergone comprehensive premarket regulatory assessment for the indication or for a critical subpopulation
EUAL: Not Prequalification

Submission requirements for each product type identified in respective guidance documents

Applicants are encouraged to contact WHO as early as possible to discuss specifics of their application

Applicant must attest intention to complete development and apply for WHO prequalification
EUAL Dx

Where possible, the EUAL for IVDs process consists of:

• A desktop review of selected manufacturing and QMS documentation;

• A review of any existing documentary evidence of safety and performance; and

• A limited laboratory evaluation of relevant performance and operational characteristics of the product.
EUAL Dx – Content of the application

Evidence of implementation of a manufacturing QMS
- ISO 13485:2003 certificate
- most recent regulatory audit report,
- quality manual,
- exclusions or non-applications,
- list of valid quality management documentation,
- management review report

Details of production

Critical supplier list

Details on the experience with the product

Details on the manufacturing capacity
EUAL Dx – Content of the application

Complete set of labels

Product Performance Specification, and Associated Validation and Verification Studies - relevant to support the intended use.

- Specimen type
- Trueness and precision studies.
- Analytical sensitivity and specificity: interference and cross reactivity studies.
- Traceability of calibrators and control material values
- Measuring range of the assay:
- Validation of assay cut-off:
- Validation of assay procedure – reading time:
- Claimed shelf life, In-use stability and Shipping stability
- Robustness Studies
- Clinical evidence (clinical or diagnostic sensitivity and specificity)
EUAL Dx – Abbreviated Assessment

Some submissions submitted for WHO EUAL may have undergone a simultaneous assessment through other similar Member State emergency mechanisms.

In situations where independently generated performance data are available generated using a suitable reference assay, WHO will consider using these data to reduce the extent of a WHO-coordinated performance evaluation.
EUAL Dx – Ad Hoc Advisory Committee for the Emergency Use of IVDs (AACEUD)

*May* be convened to assess the information in the product EUAL application and other available information.

When requested, will issue an opinion on the acceptability of the IVD for emergency use in the context of the public health emergency. This opinion will be advisory to WHO.

Will not be involved in procurement decisions.
EUAL – Decision on Emergency Use Listing

If decision is to list the product, WHO will publish information about the IVD in a public report available on the WHO website.

The validity of a listing will generally be for 12 months.

All decisions will be reassessed within 12 months (or sooner, if further data become available that could alter the original opinion).
EUAL Dx – Post Market Surveillance for IVDs

For EUAL listed IVDs, appropriate post-market surveillance mechanisms should be in place to allow for the timely notification and evaluation of adverse events to WHO and the relevant NRAs.

The WHO IVD complaint form should be completed as much as possible and sent to WHO. The form is available at the following WHO web address

http://www.who.int/diagnostics_laboratory/postmarket/en/

Manufacturers must notify national regulatory authorities and WHO of adverse events associated with the use of a product in the EUAL.
EUAL Dx—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
EUAM Dx – International Collaboration for Ebola

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 based Lab and Field evaluations

- BSL4 lab and LOD studies (Bernhard Nocht Inst, Germany)
- Sierra Leone clinical performance study (Nigerian and PHE Labs)
EUAL Dx – Current Listings

Ag Assays
- SD Q Line Ebola Zaire Ag
- ReEBOV™ Antigen Rapid Test Kit

NAT Assays
- FilmArray™ Biothreat-E
- XpertR Ebola Test
- Liferiver™ – Ebola Virus (EBOV) Real Time RT-PCR Kit
- RealStar Filovirus Screen RT-PCT Kit 1.0
EUAL Dx – Current Listings

Ag Assays
- SD Q Line Ebola Zaire Ag
- ReEBOV™ Antigen Rapid Test Kit
- One Step Ebola Test

NAT Assays
- FilmArray™ Biothreat-E
- XpertR Ebola Test
- Liferiver™ – Ebola Virus (EBOV) Real Time RT-PCR Kit
- RealStar Filovirus Screen RT-PCT Kit 1.0
EUAL Dx– In the field for Ebola

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
Non-infectious synthetic Ebola RNA references
Reference reagents for calibration of secondary reference material established by the WHO ECBS.

- EBOV RNA NP-VP35-GP WHO Reference Reagent (NIBSC code 15/222)
- EBOV RNA VP40-L WHO Reference Reagent (NIBSC code 15/224),

Low-positive in-run controls for monitoring the analytical sensitivity of NATs
- (NIBSC codes 15/136 and 15/138).

In run control material for Ag assays currently being developed
EUAL Dx – Why its needed

- Enquiry for information on a rapid test being promoted in West Africa resulted in, amongst other actions, WHO informing FDA

- FDA compliance team identified manufacturer on the US west coast illegally manufacturing and exporting EVD IVDs of unknown quality
EBOLA Phase 3 – Surveillance Phase

• The purpose of this Phase 3 framework is to incorporate new knowledge and tools into the ongoing Ebola response and recovery work to achieve and sustain a “resilient zero”.

• Phase 3 of the response builds upon the rapid scale-up of treatment beds, safe and dignified burial teams, and behaviour change capacities during Phase 1 (August – December 2014), and the enhanced capacities for case finding, contract tracing, and community engagement during Phase 2 (January to July 2015).