Emergency Use Assessment and Listing

Zika virus (ZIKV)

On 1 February 2016, WHO’s Director General announced that the strong association, in time and place, between infection with the Zika virus and a rise in detected cases of congenital malformations and neurological complications constituted a Public Health Emergency of International Concern (PHEIC). On 5 February 2016 the WHO Prequalification Team announced that the Emergency Use Assessment and Listing Procedure (EUAL) established during the 2014 Ebola Virus Disease outbreak was now open to candidate in vitro diagnostics (IVDs) intended for Zika virus diagnosis.

The EUAL procedure was developed to assist procurement agencies and Member States with selection of IVDs for procurement related to a PHEIC. It does so by assessing against current WHO/international standards, where available, whether evidence submitted for a specific IVD is sufficient to demonstrate that the benefits of its use outweigh any foreseeable risks and uncertainties within the context of a given PHEIC.

EUAL assessment consists of three steps:
1. review of the manufacturer’s quality management system (QMS) documentation;
2. review of the documentary evidence of safety and performance, including labelling and product performance specifications, and associated verification and validation studies;
3. performance evaluation of limited scope to verify critical analytical and clinical performance characteristics.

IVDs for which each step is completed, and the results of which are acceptable, are listed for procurement.

A consultation with regulatory authorities, reference laboratories and subject matter experts was held 14–15 March 2016 in Geneva to finalize the EUAL requirements for ZIKV IVDs. The objectives of the consultation were to:

- finalize the minimal technical requirements and acceptance criteria for the documentary evidence submitted to the EUAL for Zika virus IVDs
- agree on the protocol for the evaluation of NAT-based assays for Zika virus
• agree on the protocol for evaluation of serology assays for Zika virus
• agree on the conditions that would have to be met for a potential abbreviated EUAL procedure.

The summary of the outcomes of the consultation can be viewed at the following link.

To date, WHO has received six applications from four manufacturers for ZIKV IVDs which are currently under review.

Reference laboratories have been approached to conduct the EUAL performance evaluations of the assays. Ethical clearance will be sought both by the evaluating sites and WHO from their respective ethical review boards, before conducting evaluations.

The deadline for submission of an Expression of Interest to the EUAL has been extended to 31 May 2016.

Manufacturers interested in submitting an application to the EUAL should consult the instructions for submission available on our website:
• Assays detecting Zika antibodies
• Assays detecting Zika Virus Nucleic Acid or Antigen

Weekly updates on EUAL activities conducted by the team are available on our website.

Ebola virus disease (EVD)

A new Ebola virus IVD was listed under the EUAL procedure on 24 March 2016. The OraQuick® Ebola Rapid Antigen Test Kit is an immunochromatographic single-use immunoassay for the qualitative detection of Ebola virus (EBOV) VP40 antigen, for use with whole blood and cadaveric oral fluid. More information on the product and on the outcomes of the EUAL procedure is available in the public report for the product.

On 29 March 2016, WHO’s Director General announced that the Ebola situation in West Africa no longer constitutes a Public Health Emergency of International Concern, and that the temporary recommendations adopted in response should now be terminated. Consequently, WHO will no longer accept new applications of in-vitro diagnostics (IVD) through the WHO Emergency Use Assessment and Listing (EUAL) mechanism. However, all IVD applications submitted prior to this announcement will continue to be assessed by WHO under the EUAL procedure.
EUAL and other quality assurance mechanisms for IVDs

Different processes are in place to assess the quality, safety and performance of IVDs with varying degrees of certainty, to inform UN agencies, procurement agencies and WHO Member States on procurement decisions.

The EUAL procedure is not equivalent to a full prequalification assessment and differs from the outcome of an Expert Review Panel for Diagnostics (ERPD).

EUAL is strictly applicable only in an emergency context, and thus always linked to a particular PHEIC.

WHO prequalified IVDs are eligible for procurement by WHO, WHO Member States and UN agencies, having undergone a stringent regulatory review process with a focus on the needs of resource-limited settings.

Twice a year the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) issues an Invitation to Manufacturers to Submit an Expression of Interest for Product Evaluation (EoI) by an Expert Review Panel for Diagnostics (ERPD), for a selected range of IVDs. The EoIs list products that are a priority for GFATM and UNITAID but for which too few WHO prequalified and/or stringently assessed products exist. WHO acts as the secretariat for the ERPD technical reviews. ERPD’s risk–benefit assessments help GFATM, UNITAID and other procurement agencies to take informed procurement decisions.

For more detailed information on the three different processes go to the following links:

- [WHO Prequalification of In Vitro Diagnostics](#)
- [Emergency Use Assessment and Listing](#)
- [Expert Review Panel for Diagnostics](#)

The following table summarizes the three processes:
<table>
<thead>
<tr>
<th><strong>EUAL</strong></th>
<th><strong>Prequalification Assessment</strong></th>
<th><strong>ERPD</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scope</strong></td>
<td>IVDs required during PHEIC.</td>
<td>HIV RDTs, HIV EIAs, HIV viral load, HIV early infant diagnosis and CD4 technologies, malaria RDTs, hepatitis C assays, HPV assays for use at or near point-of-care.</td>
</tr>
<tr>
<td><strong>Responsible agency</strong></td>
<td>WHO</td>
<td>WHO</td>
</tr>
<tr>
<td><strong>Timing</strong></td>
<td>In response to a declaration of a PHEIC only.</td>
<td>Rolling process; manufacturers are able to submit at any point in time.</td>
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<tr>
<td><strong>Sequence of components</strong></td>
<td>Steps are sequential.</td>
<td>Components take place in parallel.</td>
</tr>
<tr>
<td><strong>Final positive outcome</strong></td>
<td>Time-limited risk-based decision on procurement for the duration of the PHEIC.</td>
<td>WHO prequalification status. IVD is eligible for procurement by WHO, WHO Member States and UN agencies.</td>
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The three different processes address different needs and serve different purposes.
New guidance under development

WHO would like to thank manufacturers and partners who provided comments on the following documents that were posted for public comment:

- TGS-2 Establishing stability of an in vitro diagnostic for WHO Prequalification
- Sample product dossier for an IVD intended for HIV self-testing
- Reportable changes to a WHO prequalified in vitro diagnostic

All comments are now being reviewed. A final version of these documents is expected to be available in Q2 2016.

Sample Product Dossiers for HIV nucleic acid-based quantitative and qualitative assays intended for viral load monitoring and early infant diagnosis will be available on our website for public comment early Q2. We encourage manufacturers and partners to provide their comments.

Newly prequalified products

The following IVDs have been prequalified since the beginning of 2016:

<table>
<thead>
<tr>
<th>Product name</th>
<th>Manufacturer</th>
<th>Date of Prequalification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzygnost HIV Integral 4 and Supplementary reagents kit for Enzygnost®/TMB</td>
<td>Siemens Healthcare Diagnostics Products GmbH</td>
<td>24 March 2016</td>
</tr>
<tr>
<td>Enzygnost HBsAg 6.0 and Supplementary reagents kit for Enzygnost®/TMB</td>
<td>Siemens Healthcare Diagnostics Products GmbH</td>
<td>24 March 2016</td>
</tr>
<tr>
<td>AiD™ anti-HIV 1+2 ELISA</td>
<td>Beijing Wantai Biological Pharmacy Enterprise Co.</td>
<td>15 February 2016</td>
</tr>
<tr>
<td>Rapid Test for Antibody to Human Immunodeficiency Virus (HIV) (Colloidal Gold Device)</td>
<td>Beijing Wantai Biological Pharmacy Enterprise Co.</td>
<td>15 February 2016</td>
</tr>
</tbody>
</table>

See the full list of prequalified products and corresponding public reports, with a summary of the findings for each of the prequalification components (dossier review, laboratory evaluation and manufacturing site inspection).

To subscribe or unsubscribe to the Prequalification of Diagnostics Update, send an email to diagnostics@who.int with subscribe or unsubscribe in the subject.