PROCEDURE TO UPDATE THE WHO MODEL LIST OF ESSENTIAL IN VITRO DIAGNOSTICS (EDL) v.20.07.2018

I. Introduction

This procedure is to be implemented as part of the preparation for the application for test categories to be included in the second edition of the EDL in 2019 and in future editions.

The first edition of the list was launched in May 2018. It includes more than 100 types of in vitro diagnostic tests that can be used at primary health care level and in clinical laboratories, and covers a selection of disease specific and general laboratory tests.

The disease specific categories of tests were selected based on WHO guidelines for the following diseases: hepatitis, HIV, malaria, tuberculosis, syphilis and HPV. The categories of general laboratory tests were selected from other WHO guidance documents on clinical laboratories and pathology, the WHO list of priority medical devices, and disease-specific clinical guidelines.

The EDL will be updated/expanded once a year based on yearly calls for submission of applications. The WHO Strategic Advisory Group of Experts on In Vitro Diagnostics (SAGE IVD) oversees the process. The SAGE IVD is further described in Section II below.

Section III below describes the requirements for submission of applications to add categories of IVDs to the EDL, and the mechanism for reviewing these applications.

It is expected that the EDL will provide guidance and serve as a reference to Member States to develop and/or update their lists of national essential in vitro diagnostics in order to improve standardisation of, access to and proper utilisation of these tests. The EDL is also expected to contribute to health systems strengthening and advancing universal health coverage, which are central to Goal 3 of the UN Sustainable Development Goals: To ensure healthy lives and well-being for all at all ages.

In order to effectively use the EDL and adapt it to national needs, the WHO recognizes that Member States will need to consider a variety of factors. These include, among others: local demographics and patterns of diseases; training, skills and experience of available personnel; local testing gaps; the strength of local health systems; requirements for equipment and servicing; local availability of treatments; financial resources; equitable access to laboratory services; national procurement policies; supply chain management and environmental factors as well as awareness and willingness of IVD result users. To that end, information that supports the selection and use of IVDs on the EDL, such as summaries of relevant WHO clinical guidelines, selected systematic reviews, key references, indicative price information, lists of prequalified IVDs and IVDs recommended by WHO disease control departments, and other relevant resources, will be maintained on the WHO website.

A description of the SAGE IVD and the process to update the EDL is given below.
II. SAGE IVD

The WHO SAGE IVD has been established to act as an advisory body on matters of global policies and strategies related to in vitro diagnostics (IVDs). The WHO Model List of Essential IVDs (EDL) has been drawn up by the SAGE IVD in consultation with the relevant WHO clusters, the WHO Expert Committee on the Selection and Use of Essential Medicines, and other expert committee panels and technical units. In particular and as described more fully below, the Essential In Vitro Diagnostics List (EDL) will comprise categories of IVDs approved by the WHO Secretariat as recommended by the SAGE IVD pursuant to its Terms of Reference (ToR) that can be found at: http://www.who.int/medical_devices/diagnostics/sage-terms-of-reference/en/

1. The SAGE IVD will convene at least once a year to discuss and approve changes to the EDL, but will meet more often as required.

2. The experts on the SAGE IVD represent a wide range of geographical and professional backgrounds, including expertise with respect to in-vitro diagnostics (IVDs), clinical laboratory, international public health, epidemiology, clinical guideline development methodology, systematic literature search methods, national policy making on diagnostics, risk-assessment and cost-effectiveness analysis, among others. IVD users in low- and middle-income countries (LMICs) are well represented. SAGE IVD experts should be regional and gender balanced and each has completed a declaration of interest and confidentiality agreement for the process. They are to act in their own capacity and not in representation of an institution or country.

3. Meetings of the SAGE IVD are conducted in closed sessions. Observers may be invited in accordance with the WHO rules for Expert Advisory Panels and Committees to attend all or parts of the meetings of the SAGE IVD. Stakeholders, including non-governmental organizations, Member States, Missions and representatives of the IVD industry, are invited to participate in the open sessions organized during SAGE IVD meetings and to comment on the applications and draft recommendations, as discussed below. They might be consulted throughout the year for particular questions or needs of the SAGE IVD.
III. Application for inclusion of an IVD category to the EDL

The process for application is presented in figure 1 below:

1. **Application:**

Applications for inclusion of diagnostic test categories in the EDL can be submitted by, or through, relevant WHO departments, regional offices or country offices and by stakeholders, such as Member States governments, academia, Non Governmental Organizations (NGOs) as well as IVD industry and trade associations.

The application is a two step process:

**Step 1:**
The first step is a *Screening Application* which should only include the information requested in Sections 1, 2 and 3 of Box 1 (shown below). The *Screening Application* must be received at least 6 months before the next meeting of the SAGE IVD, which will take place in March 2019 (hence by 15 September 2018, and every year thereafter).

**Step 2:**
Following review of this information by WHO, successful applicants will be invited to submit a *Full Application* with the information requested in Sections 4, 5, 6, 7, 8 and 9 of Box 1. The *Full Application* should be received at least 4 months before the meeting (by 15 November 2018, and every year thereafter).

Applications should be submitted through the application form:
https://extranet.who.int/dataform/865541
Box 1. Summary of information to be included with an application for inclusion of a category of IVDs in the EDL.

### Pre-Submission (Screening Application):

**A. Only information requested in Sections 1, 2 and 3 should be included in a Screening Application for inclusion of a category of IVDs in the EDL**

1. **Applicant's information:**
   1.1. Name of the focal point in WHO submitting the application (when relevant).
   1.2. Contact person, name and information on the organisation(s) submitting the application.
   1.3. Contact person, name and information on the institutions consulted and/or supporting the application.

2. **Disease or conditions addressed:**
   2.1. Specific disease(s) or conditions targeted by the IVD category.
   2.2. Information supporting WHO public health relevance and/or clinical benefit (epidemiological information on disease burden, assessment of use, testing gaps, target population).
   2.3. Information on disease or condition: morbidity, mortality, impact on quality of life, economic impact.
   2.4. How the IVD is used: single result or part of a diagnostic testing algorithm; reference to existing WHO and/or other clinical guidelines (when available). Please provide links.

3. **IVD category description:**
   This section captures information about IVD tests available in the diagnostic test category being proposed for the EDL. The information of this section should be entered in the electronic submission tool, indicating one line per test as shown in example table in Annex 1.
   3.1. “Diagnostic test”: Test for the detection or measurement of a marker for a specific disease/s or condition/s e.g. anti-HIV-1/2; glucose.
   3.2. “Test purpose”: The reason the test is performed; diagnose, monitor, screen, other for the disease/s targeted.
   3.3. “Disease specific?”: Is the test for a single disease or condition, or is the marker relevant in multiple diseases.
   3.4. “Test format”: the types of technology used. There may be several different technologies used to test for a given marker e.g. in the case of the HIV antibody test above, it can be available as a rapid test (RDT), a manual ELISA test or a chemiluminescent immunoassay (CLIA) etc. Each should be entered in a separate row as shown in the example in Annex I.
   3.5. “Required Equipment”: e.g. None required for an RDT, or sophisticated laboratory instrument as the case may require. Include all that apply.
   3.6. “Regulatory status”: Approved by a stringent regulatory authority (SRA), WHO prequalified (WHO PQ); WHO endorsed (WHO✔); None/unknown. Include all that apply.
   3.7. “Global distribution and availability”: Are there commercial products (give examples)? NOTE: This serves to clarify global distribution for the test category being requested only. Commercial products are not named in the list.
   3.8. “List price”: Please provide range of prices in USD where available for all test formats within the IVD category. Please split the price in equipment and test components if applicable.
   Information from Section 3 should also be summarised in a table as shown in Annex I.

### Full Submission:

**B. The information requested in the following Sections 4, 5, and 6 should be described in detail in the full application for inclusion of a category of IVDs in the EDL**

4. **Typical Characteristics of IVD's in each format in which tests in the test category are available:**
   (See table in Annex I for guidance)
   4.1. Detailed description of test components (reagents/instrumentation (where relevant)), methodology and labelling for each test format available.
4.2 Diagnostic accuracy (Please provide typical sensitivity, specificity, PPV, NPV) for each test format available. Note: Sections 5.1 and 5.2 below request a summary of studies supporting performance criteria shown in this section.

4.3 “Specimen types”: Please provide the range of specimen types that can be used with each format for which the tests are available.

4.4 “Facility level”: the kind of facility in which each test format is intended to be used e.g. primary health care clinic with no laboratory (I); district/hospital laboratory (II); regional/provincial laboratory (III); national reference laboratory (IV). Include all that apply.

4.5 “User Skill level”: minimum level of training the operator undergoes to effectively perform each of the test formats: non-laboratory trained health care worker (HCW) (non-lab); laboratory trained (lab); highly skilled laboratory trained (labPlus).

4.6 “Throughput”: Number of specimens tested at one time for efficient use of each test format: high; low; single use

4.7 “Time to result”: Length of time to report the result for each test format

4.8 “Environmental stability (temperature, humidity) and shelf life”: Operating (O); Storage (S); Transport (T) for each test format.

4.9 “Disposal risks”: Risks posed by disposal of IVD components for each test format e.g. Biohazard (BioH); Toxic to humans (ToxH); Toxic to environment (ToxE); Plastic (Pl). Include all that apply.

4.10 “Quality assurance”: Please provide the following details for each test format; Control integrated into IVD (Int QC); quality control sample(s) supplied with IVD (Incl QC); quality control available separately at a cost (Sep QC);

5. In order for reviewers to determine whether there are tests available with adequate performance, quality and safety in the category being submitted, please provide an evidence summary (as available) including information requested below:

5.1 Summary of laboratory evaluation studies covering reliability and reproducibility, analytical accuracy (sensitivity, specificity); and analyses of potentially interfering substances, cross reactivity, stability, sample type. All relevant studies should be reported, detailing the search strategy and eligibility criteria used, or providing a systematic review. Please indicate the organizations responsible for conducting each of the studies and provide links to full reports for each study.

5.2 Summary of studies of clinical accuracy evaluating the test in patient pathways in clinical settings covering sensitivity, specificity, and predictive values. Full evidence of all relevant studies should be reported, detailing the search strategy and eligibility criteria used, or providing a systematic review. Please indicate the organizations responsible for conducting each of the studies and provide links to full reports for each study.

5.3 Summary of evidence of the impact of using tests in clinical practice on diagnoses, treatment, and patient outcomes. Please summarise model based evaluations and empirical studies where available and provide links to full reports.

5.4 Summary of available non-clinical data (appraisal of evidence of quality manufacturing, ease of use and test disposal) and links to any relevant references

6. Societal impact information, as appropriate

6.1 Ethical issues, (if any important ethical consideration by the type of test and consequences)

6.2 Equity and human rights issues (if it reduces inequities or increase equity and accessibility )

6.3 Acceptability (by patient or by health care worker, benefits and harms)

7. Budget and resources impact

7.1 Summary of data on comparative cost1 and cost-effectiveness, if available

7.2 Resources and budget impact on health care systems, including specialized human resources, training, maintenance issues

8. Environmental impact

9. Proposed (new/adapted) text for the EDL.

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1 All cost analyses should specify the source of the price information.
2. Review of applications and draft recommendations

A step-wise approach that will be used to review applications and draft recommendations is summarized in Box 2 and illustrated in figure 1 above.

Box 2. Review of applications for inclusion in the EDL

1. Any applications received will be analysed by the EDL Secretariat for completeness. (September)
2. Screening applications will be forwarded to the relevant WHO department(s) for evaluation to make sure they are aligned with the EDL mandate and available WHO policies and guidelines. If approved, WHO will invite the submitter to send the completed full application (Invitation mid September to be submitted to WHO by mid November)
3. Each application will be reviewed by appropriate experts selected by WHO, which may include members of SAGE IVD. These external experts will also sign a Declaration of Interests form (November to early February)
4. The full applications will be posted on the WHO website as they are received and for at least 30 days for public review and comments. Reviewers comments will also be published as they are received.
5. The applications and reviews will be presented and discussed during the SAGE IVD annual meeting. (March)
6. A recommendation and proposed text for inclusion or exclusion from the EDL will be formulated by the SAGE IVD.
7. SAGE IVD recommendations will be presented to the WHO Director-General for his consideration and approval. (May)

3. Criteria for selection of essential diagnostics for the EDL

The selection process for essential diagnostics for the EDL will include consideration of a number of factors, including:

- The public health and clinical need for the category of tests as determined for example, by disease burden and whether the proposed category of IVD tests can help to bridge an existing gap in access to diagnostics in primary healthcare facilities.
- Availability of validated commercial diagnostic tests as indicated by sound and adequate data on quality, safety, performance, and regulatory status.
- Clinical effectiveness based on published peer reviewed data, safety and comparative cost-effectiveness.
- Appropriateness of the IVD category for use at specified levels of the laboratory or health care system.
- Infrastructure level requirements, target user(s), sample type and volume, sample handling, time to results, storage conditions, operating conditions, shipping requirements, training and skill requirements, associated equipment, throughput, need for maintenance, disposal and connectivity, as appropriate.

4. Presentation of recommendations, report of the expert committee

The SAGE IVD will prepare a report summarising the reasons for each recommendation with reference to the underlying evidence. The SAGE IVD may qualify its recommendations depending on the nature of the underlying evidence. When insufficient evidence is available,

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2 See: http://www.who.int/medical_devices/diagnostics/selection_in-vitro_diagnostics/EN/
the SAGE IVD will specify that its recommendations are based on expert opinion and experience. The SAGE IVD’s report will also refer to existing standard clinical guidelines.

Immediately after the meeting and subject to final approval by the Director-General, the recommended changes to the EDL, the summary of the SAGE IVD’s considerations and other relevant information will be posted on the WHO website as part of the full report of the meeting.

The EDL secretariat can be contacted for any further information at edlsecretariat@who.int
# Annex I. Summary table for Section 3

Examples of information to be included in the table for typical commercial products in each diagnostic test category:

NOTE: The section coloured in blue represents the information required for the pre-submission. The rest of the table will only be requested for those candidates that are selected for full submission.

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Test Purpose</th>
<th>Disease Specific?</th>
<th>Test Format</th>
<th>Specimen Type(s)</th>
<th>Required Equipment</th>
<th>Facility Level</th>
<th>User Skill Level</th>
<th>Typical Throughput</th>
<th>Typical Time to result</th>
<th>Typical Storage temp</th>
<th>Regulatory status of available products</th>
<th>Typical Disposal Risks</th>
<th>Quality Assurance</th>
<th>Globally Available?</th>
<th>Approx price of test/equipment</th>
</tr>
</thead>
<tbody>
<tr>
<td>XXXXX X antigen test</td>
<td>For the diagnosis of XXXX infection</td>
<td>Yes:</td>
<td>RDT*</td>
<td>Capillary whole blood; Serum; Plasma</td>
<td>Nil</td>
<td>I, II, III</td>
<td>Non-lab</td>
<td>Single use</td>
<td>10 – 30 mins</td>
<td>O: 15 – 30°C</td>
<td>S: 2 – 30°C</td>
<td>T: 2 – 30°C</td>
<td>SRA; WHO PQ</td>
<td>BioH; Pl</td>
<td>Int QC; Sep QC</td>
</tr>
<tr>
<td>EIA**</td>
<td>Serum, plasma</td>
<td>Multiple basic automated instruments</td>
<td>II, III, IV</td>
<td>Lab</td>
<td>Low or high</td>
<td>2 hours</td>
<td>O: 15 – 25°C</td>
<td>S: 2 – 8°C</td>
<td>T: 2 – 25°C</td>
<td>SRA; WHO PQ</td>
<td>BioH; ToxE; Pl</td>
<td>Incl QC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLIA**</td>
<td>Serum, plasma</td>
<td>Single, sophisticated instrument</td>
<td>II, III, IV</td>
<td>Lab</td>
<td>Low or high</td>
<td>1.5 hours</td>
<td>O: 15 – 25°C</td>
<td>S: 2 – 8°C</td>
<td>T: 2 – 25°C</td>
<td>SRA</td>
<td>BioH; Pl</td>
<td>Sep QC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XXXXX Quant. virological</td>
<td>Monit. of response to antiviral treatment</td>
<td></td>
<td>Nucleic acid testing</td>
<td>Dried blood spot;</td>
<td>Single, sophisticated instrument</td>
<td>II; III</td>
<td>Lab</td>
<td>Single use, low or high</td>
<td>1.5 hours</td>
<td>O: 15 – 30°C</td>
<td>S: 2 – 30°C</td>
<td>T: 2 – 30°C</td>
<td>SRA; WHO PQ</td>
<td>Int QC</td>
<td></td>
</tr>
<tr>
<td>Serum; plasma</td>
<td>Single, sophisticated instrument</td>
<td>III; IV</td>
<td>LabPlus</td>
<td>High</td>
<td>5 hours</td>
<td>O: 15 – 25°C</td>
<td>S: 2 – 8°C</td>
<td>T: 2 – 25°C</td>
<td>SRA; WHO PQ</td>
<td>Int QC; Incl QC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XXXX</td>
<td>To diagnose and screen for XXXXX</td>
<td>Yes:</td>
<td>XX</td>
<td>Serum; plasma</td>
<td>Single sophisticated instrument</td>
<td>II; III; IV</td>
<td>Lab</td>
<td>High</td>
<td>XX</td>
<td>O: 15 – 25°C</td>
<td>S: 2 – 8°C</td>
<td>T: 2 – 25°C</td>
<td>SRA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*RDT: Rapid Diagnostic Test  **EIA: Enzyme Immuno Assay  ***CLIA: Chemiluminescent Immuno Assay
Annex II. Additional Resources


