World Health Organization

Background Document

Strategic Advisory Group of Experts on In Vitro Diagnostics (SAGE IVD) Meeting

Geneva, 16 to- 20 April 2018

The World Health Organization (WHO) has established Terms of Reference (TOR) for a SAGE IVD to act as an advisory body with respect to matters of global policies and strategies related to in vitro diagnostics (IVDs).

The SAGE IVD will hold its first meeting from 16 – 20 April 2018 at WHO headquarters in Geneva. The objectives of the meeting are to:

- Define the methods and the work of SAGE IVD including the way forward;
- Develop a Model List of Essential In Vitro Diagnostics (EDL);
- Determine the way forward on the EDL; and
- Provide direction/guidance for the WHO Prequalification of In Vitro Diagnostics Programme (PQ).

This document provides background materials for the SAGE IVD meeting with respect to:

- Definitions relevant to the EDL;
- Rationale and focus areas of the first EDL;
- Considerations for moving to additional iterations of the EDL;

Background on the EDL

Based on a proposal[1] by the Department of Essential Medicines and Health Products, the WHO Expert Committee on Selection and Use of Essential Medicines recommended in March 2017, the development of an EDL. In so doing, the Committee:

- acknowledged the importance of diagnostics in the context of providing appropriate medicines for patients as well as for monitoring the effectiveness or toxicity of medicines;
- suggested the use of the EML as a "model" for "its process, methodology and transparency;"
- indicated that an initial proposed focus on four disease areas: (tuberculosis [TB], malaria, HIV, and Hepatitis B &C), was appropriate, but that the list should be expanded to include diagnostics in other areas (e.g., antimicrobials and NCDs) as soon as possible; and
- suggested that the EDL should be instrumental in developing both medical guidelines and laboratory accreditation schemes in country.

The actions of the WHO Expert Committee on Selection and Use of Essential Medicines has provided initial guidance for the development of the EDL. Moving forward, the newly established SAGE IVD is now providing oversight of the EDL.

[1] WHO. Proposal for a WHO model list of essential in vitro diagnostics (or the EDL). Geneva: World Health Organization, 2017. Available at: http://www.who.int/selection_medicines/committees/expert/21/applications/essential_in-vitro_diagnostics_other/en/. Last accessed: 15/02/2018.

Definitions Relevant to the EDL

Similar to the definition of an essential medicine, the WHO recommends that essential diagnostics are defined as those that satisfy the priority health care needs of the population and are selected with due regard to disease prevalence and public health relevance, evidence of efficacy and accuracy, and comparative cost-effectiveness.

The broad term "diagnostic" include IVDs (see definition below), but also numerous other medical devices that play a role in diagnosis of diseases (e.g., imaging equipment). The generally accepted definition of a medical device used by the WHO is as follows." A **medical device** is defined as: any article, apparatus, instrument, machine, appliance, implant, reagent for in vitro use, software, material or other similar related articles, intended to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury,
- investigation, replacement, modification, or support of the anatomy or of a physiological process, supporting or sustaining life,
- control of conception,
- disinfection of medical devices,
- providing information by means of in vitro examination of specimens derived from the human body;

and does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means".[2]

Medical devices include, therefore, equipment for diagnostics, like ultrasounds, electrocardiograms, endoscopes and clinical laboratory equipment, among many others. Given the very broad nature of the diagnostics, the WHO recommends that the initial EDL address in vitro diagnostic medical devices, which are defined below.

An **IVD** is a subset of medical devices. It is defined as: a device which, whether used alone or in combination, is intended by the manufacturer for the in-vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring for compatibility purposes. It includes reagents, calibrators, control material, test kits, etc. [2]

Rationale for the EDL

Access to diagnostics is imperative for the provision of high-quality healthcare and for treatment of people around the world. But, its importance has often been overlooked.

Over the last ten years, access to treatment for people living with priority diseases such as HIV/AIDS, tuberculosis (TB), and malaria has substantially increased. However, the lack of laboratory and diagnostic capacity in resource-poor settings continues to be a barrier to achieving the treatment targets outlined by countries and by international organizations. Simpler technology that is low-cost

[2] GHTF. Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device. 2012'. Available at: http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n071-2012-definition-of-terms-120516.pdf#search=. Last accessed: 15/02/2018.

and adapted to the needs of laboratories in low- and middle-income countries (LMICs), in particular, is required in order to expand testing services to the communities that need them.

The need for improved access to testing services is particularly acute with respect to disease areas that cause significant death and morbidity in LMICs. HIV/AIDS is a good example. Testing associated with HIV includes: determining whether patients are HIV positive, and if so, whether they qualify for treatment.[3] Ongoing testing is then important to measure the status of the disease, to monitor the patient for drug toxicities, and to allow the clinician to determine when treatment is failing. With the exception of diagnosing HIV, most available testing technologies for HIV/AIDS are laboratory-based, and generally located in central laboratories in urban settings. These labs are often inaccessible to patients in peri-urban and rural areas. Decentralizing testing through the use of simpler point-of-care (POC) and near-POC technologies has the ability to drive significantly increased access for these patients.

The EDL can play a role in shining a spotlight on the importance of diagnostics and helping to improve access to testing. It can also help to focus countries on developing national essential diagnostics, and hopefully, to strengthening diagnostics systems/laboratory capacity for effective diagnostic implementation.

Proposed Focus Areas for the First EDL

In the context of the WHO Impact Framework goal of achieving 1 billion more people with coverage of essential health services by 2023, the WHO has renewed its focus on four major disease areas,: HIV, TB, malaria, and hepatitis B virus (HBV)/hepatitis C virus (HCV).[4] The goals with respect to these disease areas include: (i) at least 1 million fewer new HIV infections per year (from 1.5 million today to 500,000 in 2023); (ii) reduce TB deaths by 50% (from 1.7 million in 2016 to .85 million in 2023); (iii) reduce malaria deaths by 50% (from 429,000 in 2015 to 249,000 in 2023); and (iv) prevent a half million deaths per year from HBV and HCV related liver disease (1.34 million in 2015) to less than 830,000 in 2023). To reach these goals, diagnostics and diagnostics access for these 4 diseases must improve. [4]

WHO therefore proposes to focus the first EDL on these same disease areas in which substantial work has already been done. Of these, HIV, TB and malaria are disproportionate causes of both mortality and morbidity in LMICs, particularly in the African region. These same diseases are prominent causes of morbidity among countries in the lowest income categories. Similarly, HBV and HCV infections are significant causes of chronic liver disease, which globally causes almost 1.4 million deaths per year. WHO estimates that 248 million people are currently living with chronic HBV infection, and that another 110 million people are HCV antibody positive.[5] The burden of these two chronic infections is greatest in LMICs. [5]

[3] Note that some countries use a "test and treat" approach to HIV+ patients putting all people diagnosed HIV positive on treatment without testing for the patient's CD4 levels.

[4] WHO. Draft WHO Impact Framework: 13th General Programme of Work (11/01/2017). Geneva: World Health Organization, 2017. Available at: http://www.who.int/about/GPW13_-impact-framework-draft.pdf?ua=1. Last accessed: 15/02/2018.

[5] WHO. Guidelines on Hepatitis B and C Testing. World Health Organization: Geneva, 2017. Available at: http://www.who.int/hepatitis/publications/guidelines-hepatitis-c-b-testing/en/. Last accessed: 15/02/2018.

Recommended Diagnostics for Inclusion in first EDL for HIV, TB, malaria, and HBV/HCV.

Further supporting the focus on diagnostics associated with HIV, TB, malaria, and HBV/HCV is the fact that the WHO plays a significant role in each of these disease areas through resident disease experts and well-established programs. With respect to key diagnostics for each of these diseases, there are detailed guidelines and guidance documents available. Further, most of these diagnostics are supported by the PQ programme, which plays a role in quality assurance of key tests for HIV, malaria and HBV/HCV.

Each of the WHO disease groups covering diagnostic testing associated with HIV, TB, malaria and HBV/HCV, have made recommendations with respect to categories of diagnostics to be included in the first EDL. The categories/types of diagnostic tests recommended by each group for its disease area are provided in Annex 1.

Processes for Inclusion, Change or Deletion of Diagnostics from the EDL

Like the EML, processes must be established for the inclusion, change or deletion of diagnostics from the EDL. For the EML, such applications may be made by or via relevant departments in the WHO to the Secretary of the Committee. With respect to the EML, many applications for inclusion come from outside the WHO. The WHO recommends that like the EML, the SAGE IVD would review the applications and available data and make decisions on which diagnostics to add to, change, or delete from the EDL.

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Questions for Consideration by the SAGE IVD with Respect to the Proposed First EDL

1. What aspects need to be considered by SAGE IVD in order to support Member States?
2. What information should be provided with the list? In which format should it be provided to allow easier uptake by users?
3. How can WHO further support countries in the selection and uptake of essential in vitro diagnostics to ensure access?
4. There is a large number of potential candidates, what are the priorities?
5. Who are the experts, networks and non-state actors that can support with expertise?
6. How can candidate in vitro diagnostics be assessed in order to be considered for inclusion in the list.

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Annex 1

Draft list of diagnostics for the first WHO Essential in vitro diagnostics list

Disease	Diagnostic test	Explanation	Reference
Hepatitis B & C	Antibody (HBsAg)	Screening for HBV infection: infants over 12 months of age, children, adolescents, adults. Guidelines on hepatitis B and C testing, 2017.	Guidelines on hepatitis B and C testing February 2017: http://apps.who.int/iris/bitstream/10665/251330/1/WHO-HIV-2016.23-eng.pdf?ua=1
	Virological (HBV DNA – qualitative or quantitative)	Screening for HBV infection and monitoring of response to treatment. Guidelines on hepatitis B and C testing, 2017.	
	Antibody (anti-HCV)	Screening for HCV infection: infants over 18 months of age, children, adolescents, adults. Guidelines on hepatitis B and C testing, 2017.	
	Virological (HCV Ag or RNA – qualitative or quantitative)	Screening for active HCV infection and monitoring of response to treatment. Guidelines on hepatitis B and C testing, 2017.	
HIV	Antibody (anti-HIV) test.	Screening (for HIV infection): infants under 4 months and over 18 months of age, children, adolescents, adults. Consolidated guidelines on HIV Testing Services, July 2015.	Immunoassay formats include: rapid diagnostic tests (RDTs), other simple assays (particle agglutination), enzyme immunoassays (EIAs), chemiluminescence immunoassays (CLIA), electrochemiluminescence immunoassay (ECL) WHO list of prequalified in vitro diagnostic products: http://www.who.int/diagnostics_laboratory/evaluations/PQ_list/en/ Details can be found at: Consolidated guidelines on HIV Testing Services, July 2015. http://www.who.int/hiv/pub/guidelines/hiv-testing-services/en/ Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, 2016. http://www.who.int/hiv/pub/arv/arv-2016/en/
	Combined antibody/core antigen (anti-HIV/cAg) test.	Screening (for HIV infection). Consolidated guidelines on HIV Testing Services, July 2015.	
	Qualitative virological (HIV RNA, DNA, or US p24 Ag) test.	Screening infants under 18 months of age (for HIV infection). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, 2016.	
	Quantitative virological. (HIV RNA) test.	Monitoring (of response to antiviral treatment). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, 2016.	
	Quantitative immunological	Determination of disease status and risk of opportunistic infections. Consolidated guidelines on the use of	

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	(CD4 cell enumeration) test.	antiretroviral drugs for treating and preventing HIV infection, 2016.	
	Lateral flow urine lipoarabinomannan (LF-LAM) test.	Diagnosis and screening of active tuberculosis in people living with advanced HIV. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, 2017.	
	Cryptococcal antigen test.	Diagnosis and screening of cryptococcal meningitis in people living with advanced HIV. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, 2017.	
Malaria	Microscopy		Details can be found at: http://www.who.int/malaria/publications/diagnostic_testing/en/ http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf
	Rapid diagnostic tests (RDTs)		
Glucose-6-phosphate dehydrogenase deficiency (G6PDD)	Fuorescent spot test (FST)		http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf http://www.who.int/malaria/mpac/mpac-march2015-erg-g6pd.pdf
	Rapid diagnostic tests (RDTs)		
Tuberculosis	Sputum smear microscopy	Sputum smear microscopy on two sputum specimens remains the primary diagnostic technique in many high TB burden setting. TB programmes should transition to replacing microscopy as the initial diagnostic test with WHO-recommended rapid diagnostics (2017).	Details can be found at: Compendium of WHO guidelines and associated standards: ensuring optimum delivery of the cascade of care for patients with tuberculosis. Geneva: World Health Organization; 2017 (WHO/HTM/TB/2017.13; http://www.who.int/tb/features_archive/TB_guidelines_associated_standards/en/ Implementing tuberculosis diagnostics: policy framework. Geneva: World Health Organization; 2015 (WHO/HTM/TB/2015.11; http://apps.who.int/iris/bitstream/10665/162712/1/9789241508612_eng.pdf, Technical Expert Group Meeting Report: critical concentrations for drug susceptibility testing of medicines used in the treatment of drug-resistant tuberculosis. Geneva: World Health Organization; 2017 (WHO/HTM/TB/2017.22)
	Solid and liquid culture	Solid and liquid culture methods are suitable for central reference laboratories (regional laboratories in large countries) or intermediate-level laboratories. Liquid culture increases the case yield by approximately 10% over solid media. (2007).	
	Drug susceptibility testing (DST)	Drug susceptibility testing (DST) uses critical concentrations of anti-TB agents to determine the susceptibility or	

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Annex 1

		resistance of a culture of *M.tuberculosis* (2018 in press).	
	Xpert MTB/RIF Ultra	Xpert MTB/RIF Ultra assay should be used as the initial diagnostic test for all patients with signs and symptoms of pulmonary TB who are capable of producing sputum. This includes children who are able to provide a sputum sample and patients with extrapulmonary TB (EPTB) (2017).	
	Lateral flow urine lipoarabinomannan assay (LF-LAM)	Lateral flow urine lipoarabinomannan assay (LF-LAM) can be used to assist in the diagnostic process for HIV-positive patients who are seriously ill (2016).	
	Molecular line probe assays	Molecular line probe assays should be used as the initial test to detect resistance to isoniazid and rifampicin instead of culture-based DST(2016).	
	Molecular LPAs for second-line anti-TB agents	Molecular LPAs for second-line anti-TB agents should be used instead of phenotypic culture-based DST, as the initial test to detect resistance to fluoroquinolones and second-line injectable agents in patients with confirmed RR-TB or MDR-TB (2016).	
	Loop-mediated isothermal amplification	Loop-mediated isothermal amplification for detecting TB (TB-LAMP) may be used as a replacement test or as a follow-on test to sputum-smear microscopy for diagnosing pulmonary (2016).	
	Either TST or IGRA	Either TST or IGRA can be used for the diagnosis of latent TB infection (2018 In press).	

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