19th WHO Regulatory Update on COVID-19

02 October 2020

World Health Organization

Key Messages

Effective vaccines, diagnostics and therapeutics will be vital for ending the pandemic and accelerating the global recovery. But these life-saving tools will only be effective if they are available for the most vulnerable equitably and simultaneously in all countries. WHO has an 'emergency use and listing (EUL)' procedure which assesses novel products for use in emergency situations.

Highlights and main issues

- Two Antigen Rapid Diagnostic Tests (Ag RDTs) have been listed in the WHO EUL. Both are visually-read antigen detection assays, which do not require a specialized reader for result interpretation. Both products are intended for the qualitative detection of SARS-CoV-2 antigen in human nasopharyngeal swab specimens.
- Arrangements have been announced to make 120 million WHO EUL-listed Ag RDTs available to low- and middle-income countries (LMICs) over a period of six months.
- The first call for submission of an Expression of Interest for evaluation by the WHO (Prequalification and/or EUL) is open to candidate vaccines in phase IIb/III clinical trials that are expected to be submitted for evaluation by a National Regulatory Authority within the next 6 months.
- A public consultation has been launched on both the process and the criteria that will be used by the WHO to evaluate COVID-19 vaccines that are submitted either for PQ or for Emergency Use Listing (EUL).
- Regulators are urged to consider whether they can accept standardized labelling, bar coding and QR code options for COVID vaccines to facilitate access.
- A review has been published that summarizes the findings to date from the WHO Animal Models Working Group and provides relevant information for preclinical testing of COVID-19 vaccine candidates and therapeutics.

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Update on the ACT-Accelerator

Affordable and quality COVID-19 rapid tests for resource limited countries

A set of agreements to make available, for low and middle-income countries, affordable, high-quality COVID-19 antigen rapid tests were announced on 28 September by the Access to COVID-19 Tools (ACT) Accelerator. Organizations involved in the milestone agreement include the Africa Centres for Disease Control and Prevention (Africa CDC), the Bill & Melinda Gates Foundation, the Clinton Health Access Initiative (CHAI), the Foundation for Innovative New Diagnostics (FIND), the Global Fund, Unitaid, and the World Health Organization (WHO).

The arrangements will make 120 million antigen rapid diagnostic tests (Ag RDTs) available to LMICs – priced at a maximum of US$5 per unit – over a period of six months. These tests provide results in 15–30 minutes, rather than hours or days, and will enable expansion of testing, particularly in countries that do not have extensive laboratory facilities or trained health workers to implement molecular (polymerase-chain reaction or PCR) tests.

WHO guidance published on 11 September 2020 highlights the value of these tests in areas where community transmission is widespread and where nucleic acid amplification-based diagnostic (NAAT) testing is either unavailable or where test results are significantly delayed. FIND and WHO are working together to accelerate appropriate use by supporting implementation research that will optimize Ag RDT

use in multiple LMICs, in line with WHO guidance. This includes provision of catalytic volumes of tests to understand how Ag RDTs can best fit into health systems.

Bar codes, QR codes, labelling and traceability systems

Traceability technologies, such as two-dimensional (2D) bar-codes and quick-response (QR) codes are integrated in some national contexts for medicines and health products, but not in many other countries. Questions have been raised regarding the best options for traceability technologies for COVID-19 medicines and vaccines. Although it may not be feasible at present to consider that these technologies could be used as a universal replacement for requirements for packaging, labeling and management of vaccines and other products, regulators are asked to consider how they could fit these innovations in a national context while assuring the needs of their populations. WHO will follow-up on these issues through discussions at a regional level.

In vitro diagnostics

COVID-19 Target product profiles for priority diagnostics

The final version of Target Product Profiles (TPP) for priority COVID-19 diagnostics have been published by WHO. These TPPs describe the desirable and minimally acceptable profiles for four tests.

- Point of care test for suspected COVID-19 cases and their close contacts to diagnose acute SARS-CoV-2 infection in areas where reference assay testing is unavailable, or turnaround times obviate clinical utility
- Test for diagnosis or confirmation of acute or subacute SARS-CoV-2 infection, suitable for low or high-volume needs
- Point of care test for prior infection with SARS-CoV-2
- Test for prior infection with SARS-CoV-2 for moderate to high volume needs

These TPPs will be reviewed and updated as new information becomes available.

COVID-19 TPP for priority diagnostics (29 Sept 2020)

WHO EUL and listing update

The WHO Prequalification Unit is assessing products for Emergency Use Listing (EUL) for candidate in vitro diagnostics (IVDs) to detect SARS-CoV-2. The following IVDs are eligible for EUL submission:

- Assays for the detection of SARS-CoV-2 nucleic acid;
- Rapid diagnostic tests and enzyme immunoassays for the detection of IgM/IgG to SARS-CoV-2; and
- Rapid diagnostic tests for the detection of SARS-CoV-2 antigens.

Manufacturers interested in the EUL submission are invited to contact WHO at diagnostics@who.int and schedule a pre-submission call.

WHO EUL submissions

Applicants are asked to submit their applications for assessment based on WHO instructions and requirements for NAT and Ag detection RDTs and IVDs detecting antibodies to SARS-CoV-2 virus.

Antigen detection RDTs

Unprecedented global collaboration has enabled development and deployment of two WHO EUL-approved Ag RDT within eight months of the first identification of the virus. In comparison, it took nearly five years to develop the first RDT for HIV. Several more antigen RDTs for COVID-19 are currently under WHO EUL review. The ***Panbio COVID-19 Ag Rapid Test Device (Nasopharyngeal)*** manufactured by Abbott Rapid Diagnostics Jena GmbH and the ***STANDARD Q COVID-19 Ag Test*** manufactured by SD Biosensor, Inc. are both rapid, visually-read antigen detection assays, which do not require a specialized reader for result interpretation. Both products are intended for the qualitative detection of SARS-CoV-2 antigen (Ag) in human nasopharyngeal swab specimens. The clinical sensitivity/specificity for the STANDARD Q test is approximately 88.2%/98% and for the Panbio test 91.4%/99.8%.

IVDs listed by National Regulatory Authorities in IMDRF jurisdictions

To help countries, WHO publishes links to emergency lists, together with contact details, on IVDs authorized for use in the International Medical Device Regulators Forum (IMDRF) jurisdictions along with other useful information on policies and guidance.

The most recent update (07 Sept 2020)

Note: **WHO does not endorse any of the lists provided by NRAs. The information is provided exclusively to assist stakeholders with identifying the links to the various lists.**

Therapeutics

Research mapping of candidate therapeutics

A living research mapping of candidate COVID-19 therapeutics, displaying studies per country, showing study design, disease severity in study participants, and type of treatment being studied, as well as network maps of these studies, has been made available at: https://www.covid-nma.com/dataviz/

Living synthesis of Covid-19 study results

A list of treatment comparisons, a summary of the evidence for that comparison, and a detailed description of primary studies, including a risk of bias assessment is at: https://covid-nma.com/living_data/index.php

Adverse drug reactions

EMA's safety committee (Pharmacovigilance Risk Assessment Committee) has started a review of a safety signal to assess reports of acute kidney injury in some patients with COVID-19 taking Veklury (remdesivir). Remdesivir is so far the only antiviral drug that has shown positive effects on complications of the COVID19 disease.

Numerous other suggested treatments still lack reliable information on efficacy in COVID-19. The current pharmacovigilance update therefore focuses mainly on remdesivir. In addition, the COVID-19 related adverse events reporting (AE) in VigiBase for two other medicines, favipiravir and ivermectin, has now passed the threshold of 100.

A full overview of the COVID-19 AE reporting

Vaccines

First call to manufacturers of vaccines against COVID-19

The first call for submission of an expression of interest (EOI) is open to candidate vaccines in phase IIb/III clinical trials that are expected to be submitted for evaluation by a National Regulatory Authority within the next 6 months. Priority will be given to candidate vaccines that are expected to meet all or most of the WHO published TPP characteristics. Those EOIs that are considered acceptable to proceed with the submission of a dossier, will be assessed according to either the EUL procedure or PQ, using relevant guidance in the WHO Technical Report Series and draft evaluation criteria for COVID-19 vaccines.

Expression of Interest (EOI) for evaluation by the WHO (Prequalification and/or EUL)

Draft considerations for evaluation of COVID-19 vaccines for WHO EUL

A public consultation has been launched on both the process and the criteria that will be used by the WHO to evaluate COVID-19 vaccines that are submitted either for PQ or for Emergency Use Listing (EUL). The current status of development of a candidate Covid-19 vaccine, the extent of the available quality, safety and efficacy data and regulatory approvals by relevant NRAs will guide WHO's decision on which pathway (PQ or EUL) to follow for each vaccine. The document provides advice to manufacturers on criteria that will be used to assess clinical trial design, endpoints, and statistical criteria are described. Specific data that should be submitted to answer programmatically relevant questions are outlined. Manufacturing, quality control and labelling requirements are summarized, as are non-clinical data to address the potential for vaccine-associated enhanced disease. Post-authorization commitments are specified.

Please send comments in writing to WHOEUL@who.int no later than **08 October 2020, 18:00 CET**

Considerations for evaluation of COVID-19 vaccines

EMA starts first rolling review of a COVID-19 vaccine in the EU

EMA's human medicines committee (CHMP) has started the first 'rolling review' of a COVID-19 vaccine, which is being developed by the company AstraZeneca in collaboration with the University of Oxford. The start of the rolling review means that the committee has started evaluating the first batch of data on the vaccine, which come from laboratory studies (non-clinical data). This does not mean that a conclusion can be reached yet on the vaccine's safety and effectiveness, as much of the evidence is still to be submitted to the committee. The CHMP's decision to start the rolling review of the vaccine is based on preliminary results from non-clinical and early clinical studies suggesting that the vaccine triggers the production of antibodies and T cells (cells of the immune system, the body's natural defenses) that target the virus. Large-scale clinical trials involving several thousands of people are ongoing, and results will become available over the coming weeks and months.

EMA will complete its assessment according to its usual standards for quality, safety and effectiveness. While the overall review timeline cannot be forecast yet, the process should be shorter than a regular evaluation due to the time gained during the rolling review.

More information on EMA's rolling review

Living mapping and living systematic review of COVID-19 studies

Living mapping and living systematic reviews are available based on daily searches of the literature for candidate vaccines against COVID-19.

The tool allows vaccine comparisons where data are available as well as **a table** with the general characteristics of each trial. For each vaccine comparison, forest plots for all the outcomes of interest are available as well as the Summary of Findings table.

The mapping tool is available at: https://covid-nma.com/vaccines/mapping/

Landscape of candidate vaccines for SARS-CoV-2

A landscape analysis of candidate SARS-CoV-2 vaccines is regularly published by WHO. Currently, over 180 vaccines are at some stage of development. Of these, **41 vaccine candidates are in human trial**. About 10 are in or entering phase III trials. There are several others currently in phase I/II, which will enter phase III in the coming 2 months. This is a very robust pipeline – the more candidates, the more opportunities for success (typically success rate of candidate vaccines is 10%). The candidate vaccines are of various types – virus vaccines using live attenuated virus, viral vector vaccines, protein-based vaccines, and nucleic acid or RNA and DNA vaccines, which are completely new platforms.

A landscape analysis of candidate SARS-CoV-2 vaccines is regularly published by WHO.

Landscape of COVID-19 candidate vaccines (02 Oct 2020)

Research protocols, assays and reference standards

WHO Working Group: Assays and reference preparations

The evolution of the immune response after mild (non-hospitalized) SARS-CoV-2 infection was described in the 30 September meeting. A cohort of 64 participants, median age 55 years, were followed longitudinally. The neutralizing antibody showed a two-phase decay with an initial rapid decline over the first 70 days after which the decay slowed and stabilized. The half-life was estimated to be 519 days. The early decay was shown to be due to a rapid decline in spike-specific IgA and IgM.

In contrast, IgG binding to spike protein remained stable and persisted. Indeed, IgG memory B cells were shown to increase with time and to mature to a resting cell phenotype. These patterns are consistent with the evolution of the immune response for many other virus infections.

WHO Working Group: Animal models

In February 2020 the WHO assembled an international panel of experts to develop animal models for COVID-19 to accelerate testing of vaccines and therapeutics. A review has been published that summarizes the findings to date and provides relevant information for preclinical testing of COVID-19 vaccine candidates and therapeutics. A number of small and large animal models that investigators can utilize to explore important aspects of COVID-19, including pathology, transmission, and host responses to SARS-CoV-2, as well as the safety and efficacy of potential therapeutics or vaccines.

Mouse models, Syrian hamster models, ferret models, and non-human primate models are extensively discussed, as well as experiments in mink, cats, dogs, pigs, chickens, ducks and fruit bats. Future studies will need to standardize challenge stocks, assays, and protocols to allow comparisons of different candidate interventions. Animal model are still needed to assess VAERD, and the establishment of a positive control for VAERD will be important.

Animal models for COVID-19

Medical Devices

WHO Medical devices September 2020 newsletter

WHO Medical Devices Newsletter

The latest version of the newsletter includes updates on new documents released in September, including an update to the Emergency Global Supply catalogue. The draft specifications listed will be integrated in a single publication along with other sets that are being updated, including PPE, and will be available in October.

The newsletter also provides information on facility surveys, country surveys, on-line training, and short-term consultancies available at WHO.

The newsletter is available by sending an email to: LISTSERV@listserv.who.int with the words: SUBSCRIBE WHOMEDICALDEVICES in the body of the message.

For requests and questions, contact Adriana Velazquez at COVID-MED-DEVICES@who.int