23rd WHO Regulatory Update on COVID-19

27 November 2020

World Health Organization

Key Messages

WHO's assessment of candidate COVID-19 vaccines by the Prequalification Team has started, with experts from different regions included in a global assessment team. WHO will ensure that its assessment of these vaccines is robust, representative and facilitates timely access at the country level. For vaccines that achieve emergency use listing or prequalification by WHO, support to facilitate national level approval processes will be offered to countries in product specific roadmaps and regulatory preparedness plans outlined in WHO Interim Guidance on National Deployment and Vaccination Planning.

Highlights and main issues

- New information and clinical recommendations on remdesivir are presented in an updated version of the WHO living guideline on therapeutics and COVID-19. A panel convened by WHO made a conditional recommendation against the use of remdesivir in hospitalized patients with COVID-19, regardless of disease severity.
- On the basis of the WHO recommendation against the use of remdesivir, remdesivir was suspended from the WHO list of prequalified medicinal products and both a finished pharmaceutical product and an active pharmaceutical ingredient of remdesivir were removed from the invitations to manufacturers to submit Expression of Interests for prequalification (PQ).
- The US FDA has issued an Emergency Use Authorization for casirivimab and imdevimab, administered together, for the treatment of mild to moderate COVID-19.
- Advice to manufacturers 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) has been published.
- WHO Guidance on National Deployment and Vaccination Planning, which is intended to help countries develop their plan for COVID-19 vaccine introduction, has been published.
- The European Medicines Agency has published a safety monitoring plan and guidance on risk management planning for COVID-19 vaccines.
- A COVAX workshop on 19 November reviewed current knowledge on natural and vaccine induced immune responses, relevant available assays, and clinical trial designs. The workshop was convened to help identification of an immune correlate of protection that could accelerate access to follow-on COVID-19 vaccines and support evaluation of durability of protection for each vaccine.
- Two major international collaborative studies have concluded, respectively, that a SARS CoV-2 antibody preparation and a SARS CoV-2 RNA preparation are both suitable to be established as WHO International Standards. The results of the two international collaborative studies have been published for public scrutiny. Comments are requested by 3

December 2020.

- An updated WHO model reference list of basic and priority medical devices required for the COVID-19 response, following the latest available evidence on COVID-19 clinical management and infection prevention and control, has been published.
- A new WHO document provides interim guidance on the quality, performance characteristics and related standards of personal protective equipment (PPE) to be used in the context of COVID-19.
- A number of institutions and organizations have expressed concern that the threat of substandard/falsified Covid19 vaccines is overlooked.

Contents

Update on the ACT-Accelerator

Guidance on developing a national deployment and vaccination plan for COVID-19 vaccines

This WHO Interim Guidance is intended to help countries develop their plan for COVID-19 vaccine introduction. The guidance is built upon existing documents and the core principles of the WHO Strategic Advisory Group of Experts (SAGE) values framework for the allocation and prioritization of COVID-19 vaccination, the prioritization roadmap, and the fair allocation mechanism for COVID-19 vaccines through the COVAX Facility and will be continually shaped by the vaccine-specific recommendations.

The guidance is based upon key assumptions, and best available evidence at the time of writing. There is a high likelihood that these assumptions will require updating over time due to the evolving situation and therefore should not be considered final. Once a vaccine, or vaccines, is closer to approval and more is understood about its properties, this guidance document will be updated.

The guidance includes sections on regulatory preparedness, and vaccine safety monitoring, including management of adverse events following immunization and injection safety. The document will soon be available in all UN languages together with a corresponding power-point deck for orientation.

> Guidance on developing a national deployment and vaccination plan for COVID-19 vaccines, Interim Guidance (16 Nov 2020)

In vitro diagnostics

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.

So far, 24 products have been listed as eligible for WHO procurement among 55 expressions of interest for NAT assays, 32 for antibody detection assays and 9 for antigen detection RDTs have been received.

> EUL listed IVDs
>
> The status of each EUL application (25 Nov 2020)

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 (23 Nov 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

WHO Living Guideline: Therapeutics and COVID-19

New information and clinical recommendations on remdesivir are presented in an updated version of the WHO living guideline on therapeutics and COVID-19. Remdesivir is increasingly used to treat patients hospitalized with COVID-19 and is of considerable interest to all stakeholder groups. However, a panel convened by WHO made a conditional recommendation against the use of remdesivir in hospitalized patients with COVID-19, regardless of disease severity.

The recommendation on remdesivir was informed by results from a systematic review and network meta-analysis (NMA) that pooled data from four randomized trials with 7333 participants hospitalized for COVID-19. The resulting GRADE evidence summary suggested that remdesivir has possibly no effect on mortality (odds ratio 0.90, 95% confidence interval [CI] 0.70 - 1.12; absolute effect estimate 10 fewer deaths per 1000 patients, 95% CI from 29 fewer - 11 more deaths per 1000 patients; low certainty evidence); and possibly no effect on the other important outcomes identified by the panel, with similar low to very low certainty of evidence. The panel judged the overall credibility of subgroup analyses assessing differences in mortality by severity of illness to be insufficient to make subgroup recommendations.

Considering the low or very low certainty evidence for all outcomes, the panel concluded that the evidence did not prove that remdesivir has no benefit; rather, there is no evidence based on currently available data that it does improve patient-important outcomes. The panel placed low value on small and uncertain benefits in the presence of the remaining possibility of important harms. In addition, the panel considered contextual factors such as resources, feasibility, acceptability and equity for countries and health care systems.

Therapeutics and COVID-19: living guideline (20 Nov 2020)

Remdesivir removed from the PQ Invitations for Expression of Interest

On the basis of the WHO recommendation against the use of remdesivir, the WHO Prequalification (PQ) Unit removed remdesivir, as either a finished pharmaceutical product or an active pharmaceutical ingredient, from the invitations to manufacturers to submit expression of interests for PQ.

Casirivimab and imdevimab, administered together, receive US FDA emergency use approval (EUA)

Based on an assessment of a randomized, double-blind, placebo-controlled clinical trial in 799 non-hospitalized adults with mild to moderate COVID-19 symptoms the US FDA has issued an EUA for casirivimab and imdevimab, administered together, for the treatment of mild to moderate COVID-19.

Viral load reduction in patients treated with casirivimab and imdevimab was larger than in patients treated with placebo at day seven. For patients at high risk for disease progression, hospitalizations and

emergency room visits occurred in 3% of casirivimab and imdevimab-treated patients on average compared to 9% in placebo-treated patients. Casirivimab and imdevimab must be administered together by intravenous (IV) infusion.

Casirivimab and imdevimab are not authorized for patients who are hospitalized due to COVID-19 or require oxygen therapy due to COVID-19.

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

Vaccines

Considerations for the assessment of COVID-19 vaccines for WHO PQ or EUL

Advice to manufacturers on both the process and the criteria that will be used by the WHO to evaluate COVID-19 vaccines that are submitted either for prequalification (PQ) or for Emergency Use Listing (EUL) has been published. 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 submission and review processes are described. Only vaccines that have undergone phase IIb or phase III studies and have received authorization from a reference National Regulatory Authority (NRA) should be submitted for consideration. 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.

Considerations for the Assessment of COVID-19 Vaccines for Listing by WHO (25 Nov 2020)

Regulatory and WHO EUL/PQ assessments of candidate COVID-19 vaccines underway

Interim analyses of phase 3 studies have been announced, through press releases, for four candidate COVID-19 vaccines. These are the mRNA platform candidates from Pfizer/Biontech and Moderna, the ChAdOx1 platform candidate from AstraZeneca, and the Ad26/Ad5 platform candidate from the Gamaleya National Centre. Preliminary point estimates of vaccine efficacy all exceed WHO Target product Profiles and WHO draft EUL criteria. No safety concerns have been identified from the preliminary analyses. Uncertainties remain, however, since the full data have not yet been assessed by regulators nor have peer-reviewed manuscripts yet been published.

Regulators are receiving rolling submissions of data packages, which are being assessed as they are submitted. WHO EUL/PQ are also reviewing rolling submissions in parallel using, where feasible, the principles of regulatory reliance through collaboration with the NRA of record. WHO's assessment of

these vaccines includes experts from different regions and will also be followed by facilitation of the national approval process for those vaccines that are listed by WHO. The WHO will ensure that the assessment of these vaccines is robust, representative and facilitates timely access at the country level.

EMA's safety monitoring plan and guidance on risk management planning

EMA and the national authorities in EU Member States have prepared a safety monitoring plan for COVID-19 vaccines. The plan outlines how relevant new information emerging after the authorization and uptake of COVID-19 vaccines in the pandemic situation will be collected and promptly reviewed. Through the implementation of these activities, the EU medicines regulatory network will assess any safety data emerging from a range of different sources (spontaneous reporting, observational studies, etc.). Any potential safety concerns identified will be addressed by taking appropriate regulatory action to safeguard individual and public health and communicating with the public in a transparent and timely manner. The plan comprises new reporting obligations for companies that will have to submit monthly safety reporting summaries in addition to the regular updates foreseen by the legislation. Furthermore, the plan details the scientific studies already in place to monitor the safety, effectiveness and coverage of COVID-19 vaccines after their authorization.

EMA has also published guidance to support companies' preparation of risk management plans (RMPs) for COVID-19 vaccines. As for any medicine, companies applying for approval for COVID-19 vaccines must submit RMPs. The RMP explains how the company must monitor and report on the safety of the vaccine once authorized, and what measures it must put in place to further characterize and manage risks. RMPs are updated as new information becomes available.

To maximize the transparency of regulatory activities, all RMPs for COVID vaccines will be published on the EMAs website.

> EMA publication of safety monitoring plan and guidance on risk management planning for COVID-19 vaccines (13 Nov 2020)

Product specific guidelines for batch release of COVID-19 vaccines

The European Directorate for the Quality of Medicines and Healthcare (EDQM) has published three product-specific guidelines for batch release of the following pandemic COVID-19 vaccine platforms: non-replicating chimpanzee adenovirus-vectored vaccines; non-replicating human adenovirus-vectored vaccines; and mRNA vaccines. The guidelines have been prepared based on current knowledge. Once the relevant marketing authorizations have been approved they will be reviewed and updated accordingly including addition of a model protocol for the manufacturer's data submission. The availability of these guidelines at an early stage will help anticipate the launch of the first vaccines and allow batch-releasing laboratories and manufacturers to take the necessary steps to prepare for batch release by the European network of national control laboratories, thus preventing delays in availability while still ensuring their quality and safety.

> Official Control Authority Batch Release (OCABR) guidelines for pandemic COVID-19 vaccines

COVID-19 correlates of protection workshop

Correlates of protection for COVID-19 are being studied intensively as results from initial vaccine efficacy trials become available. Identification of an immune correlate of protection could accelerate access to follow-on COVID-19 vaccines and support evaluation of durability of protection for each vaccine. A COVAX workshop on 19 November reviewed current knowledge on natural and vaccine induced immune responses, relevant available assays, and clinical trial designs. There was strong endorsement in the workshop, based on preliminary evidence, of the neutralizing antibody titre as a candidate

correlate. There was also strong promotion for neutralizing antibody titres to be expressed relative to the candidate WHO International Standard for anti-SARS CoV2 antibody, contingent upon the reagent being established by WHO in early December. The continued need to analyze efficacy and immune response data from additional vaccine platform technologies was also stressed, as was the need to continue to investigate longer term immune responses for all vaccine platforms.

Presentations are available at COVAX SWAT team on Clinical development and Operations

Upcoming Meeting: Vaccines and Related Biological Products Advisory Committee

On December 10, 2020, the US FDA's Center for Biologics Evaluation and Research's (CBER) Vaccines and Related Biological Products Advisory Committee (VRBPAC) will meet in open session to discuss Emergency Use Authorization (EUA) of the Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 in individuals 16 years of age and older.

FDA intends to make background material available to the public no later than 2 business days before the meeting. If FDA is unable to post the background material on its website prior to the meeting, any background material will be made publicly available at the time of the advisory committee meeting, and additional materials will be posted on FDA's website after the meeting.

Announcement of the CBER VRBPAC meeting on 10 Dec 2020

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 200 vaccines are at some stage of development. Of these, **48 vaccine candidates are in human trial**. About 11 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 (12 Nov 2020)

Research protocols, assays and reference standards

Candidate WHO International Standards for SARS CoV-2 antibodies and RNA

Two major international collaborative studies have concluded, respectively, that a SARS CoV-2 antibody preparation and a SARS CoV-2 RNA preparation are both suitable to be established as WHO

International Standards. These reagents are intended as global references against which national reference preparations would be calibrated. Calibration of national references against a single global standard will facilitate comparison of results of assays (e.g. of the antibody response to candidate COVID vaccines) conducted in different countries. The development and scientific assessment through collaborative study of these reagents has been completed in record time.

The results of the two international collaborative studies have been published for public scrutiny.

Public consultation is open until 3 December 2020:

> Collaborative Study for the Establishment of a WHO International Standard for SARS-CoV-2 RNA
>
> Establishment of the WHO International Standard and Reference Panel for anti-SARS-CoV-2 antibody

Comments received by 3 December 2020 will be considered in the preparation of discussions at the coming WHO Expert Committee on Biological Standardization meeting to be held in December 2020.

WHO Working Group: Assays and reference preparations

A study that investigated the association between antibodies to SARS CoV-2 and protection against reinfection was presented at the 25 November meeting. Although there have been more than 50 million infections worldwide, there have been very few documented reinfections, suggesting post-infection immunity is effective, at least in the short-term. A longitudinal study followed healthcare workers, with PCR testing every 2 weeks and serology testing every 2 months. Anti-spike and anti-nucleocapsid antibodies were associated with protection against reinfection for a period of 6 months.

Substandard and falsified products

A number of institutions and organizations have expressed concern that the threat of substandard and falsified (SF) Covid-19 vaccines is overlooked. The more SF medical products reach patients, the more this will erode trust in systems. Covid19 has showed how much confidence in authorities, in health systems, in the experts, is essential to achieve compliance with public health guidelines. The fundamental issue is trust: just as patients need to be able to trust in health workers expertise, health workers need to be able to trust that products they prescribe and dispense actually do what they are meant to do: prevent or treat illness and improve people's health.

WHO expects to issue an alert on falsified Harvoni (Ledipasvir/sofosbuvir) in the near future. The COVID-19 pandemic continues to disrupt markets and divert resources from pre-existing diseases and needs. For example, a Malaria Gamechangers online roundtable on Medicine Quality and Innovations to detect SF medicines in Asia Pacific will discuss how the COVID-19 pandemic exacerbates the issue (02 Dec 2020).

WHO continues to receive reports of SF medical products related to COVID-19, including dexamethasone. Regulatory authorities are strongly encouraged to report any suspicions of SF medical products to WHO (rapidalert@who.int), regardless of whether the product may have already been reported. This is the only way we can evidence the scope, scale and harm caused by SF medical products – and provide substantive response support to Member States.

Supply chain

Shortages

With the second wave of COVID-19 affecting many countries, shortages of ICU medicines are

anticipated. The most recent report is a shortage of porcine-derived heparin. The root causes are complex and relate to increased demand for treatment of COVID-19 as well as a history of chronic shortage related to the active pharmaceutical ingredient (API).

The API has been in frequent shortage due to disease outbreaks and contamination problems, and the market has been slow to recover. There are no reported problems with bovine-derived heparin; however, this product has a more limited use base and the manufacturing base and number of countries with marketing authorizations for this product declined sharply in the 1990s.

This shortage disproportionately affects low- and middle-income countries. They have more limited access to newer anti-coagulants, including dabigatran, rivaroxaban, and apixaban, which were recently included in the WHO Model List of Essential Medicines.

Traceability technologies for use with emergency products:

A working document was circulated in recent weeks, and based on comments received, a revised version will be released in the next two weeks. Any additional comments on the existing document may be sent directly to hedmanL@who.int, using the subject heading “traceability COVID”.

Watch list and active shortages

WHO is still maintaining a watch list on the following products. There are not active reports of shortages, but the watch list remains in force:

- Antibiotics: azithromycin, levofloxacin, metronidazole, amoxiclav, piperacillin, tazobactam
- epinephrine and norepinephrine
- Benzodiazepine sedatives: midazolam and lorazepam
- Nonbenzodiazepine sedatives: propofol
- Antipsychotics: haloperidol
- Neuromuscular relaxants: succinylcholine, atracurium, or vecuronium.
- Opioids: morphine and fentanyl
- Malaria treatments: hydroxychloroquine, chloroquine, artemether-lumefantrine, artemisinin-based combination therapies, sulfadoxine-pyrimethamine + amodiaquine)
- NCD: Metformin and insulin
- Antipyretics: paracetamol (aka acetaminophen)
- PPE
- Oxygen and related equipment
- Ventilators

The following medicines remain in shortage, with WHO working with suppliers on potential solutions:

- Porcine-derived heparin
- Influenza vaccines

The following medicine has been removed from the watch list based on the WHO decision to discontinue recommendations for its use in treating COVID-19.

- Experimental medicines: remdesivir

Medical Devices

WHO Interim Guidance on Priority medical devices list for the COVID-19 response

An updated WHO model reference list of basic and priority medical devices required for the COVID-19 response, following the latest available evidence on COVID-19 clinical management and infection prevention and control, has been published. This replaces the first version of the WHO list, which was published 9 April 2020. The list includes associated technical specifications describing quality and performance characteristics of the priority medical devices in order to support the incorporation, procurement, lease or donation of these products.

> Priority medical devices list for the COVID-19 response and associated technical specifications: Interim Guidance (19 Nov 2020)

Technical specifications of personal protective equipment for COVID-19

A new WHO document provides interim guidance on the quality, performance characteristics and related standards of personal protective equipment (PPE) to be used in the context of COVID-19. This includes WHO Priority Medical Devices, specifically: surgical masks, non-surgical masks, gloves, goggles, face shields, gowns and N95 masks. It is intended for procurement agencies, occupational health departments, infection prevention and control departments or focal points, health facility administrators, biomedical and materials engineering, PPE manufacturers and public health authorities at both national and facility levels.

> Technical specifications of personal protective equipment for COVID-19 (13 Nov 2020)

WHO Medical Devices November 2020 Newsletter

The Newsletter includes updates on new documents released in November and 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 WHO MEDICAL DEVICES in the body of the message.

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