



Key Messages

WHO will not validate any vaccine unless it is proven safe and effective. WHO welcomes the encouraging press announcements of COVID-19 vaccines that have 90% effectiveness, and look forward to reviewing the data. Safe and effective vaccines are one of the important tools to fight the COVID-19 pandemic. We must work in solidarity to get the best possible products in the least possible time and make those safe and effective products available to as many people as possible around the world, ethically and equitably.

Highlights and main issues

- WHO and ICMRA, as outlined in a joint statement, have committed to a series of actions to improve global regulatory alignment.
- To promote global regulatory alignment in the evaluation of COVID-19 vaccine candidates, WHO provided a briefing on COVAX, including potential timelines for PQ/EUL decisions and issues that may arise during dossier review, at the 12 November ICMRA Policy meeting. The WHO working position on labelling, barcodes and QR codes was also shared.
- The US FDA has issued an Emergency Use Authorization (EUA) for bamlanivimab, a neutralizing IgG1 monoclonal antibody that binds to the receptor binding domain of the spike protein of SARS-CoV-2, for the treatment of mild to moderate COVID-19
- A mobile application called “Med Safety”, has been jointly launched in nine countries with the Uppsala Monitoring Centre in Sweden and the UK Medicines and Healthcare products Regulatory Agency. The app enables health-care professionals and patients to report suspected adverse reactions directly to the national authorities’ data base. WHO is preparing to roll out the app in more countries once a COVID-19 vaccine becomes available.
- Based on the first interim efficacy analysis Pfizer Inc and BioNTech Se announced their mRNA-based vaccine candidate against SARS-CoV-2, BNT162b2, has demonstrated evidence of 90% efficacy against COVID-19 in participants without prior evidence of SARS-CoV-2 infection. The data will be discussed with regulatory authorities worldwide.
- To support countries in planning, a WHO Roadmap has been published of public health strategies and target priority groups for vaccination for different levels of vaccine availability and epidemiologic settings.
- A WHO Medical product alert was issued on falsified influenza vaccine. Demand on influenza vaccines is high this year as WHO experts have called for health workers and older adults to be considered as the highest priority risk groups to receive influenza vaccines during the COVID-19 pandemic.

Contents

Key Messages.....	1
Highlights and main issues.....	1
Update on the ACT-Accelerator	2
Development of WHO living guideline and evaluation timelines for EUL/PQ procedures.....	2
UNICEF and PAHO joint COVID-19 vaccine tender on behalf of COVAX Facility	3
COVAX briefing to ICMRA COVID-19 policy group	3
Alignment of approaches by regulators	3
ICMRA/WHO joint statement.....	3
Draft WHO Guidance on Good manufacturing practices for investigational products	3
Draft WHO Guidance on Good practices for research and development facilities	4
<i>In vitro</i> diagnostics.....	4
WHO EUL and listing update.....	4
Implementation project on SARS-CoV-2 Antigen detecting rapid diagnostic test.....	5
IVDs listed by National Regulatory Authorities in IMDRF jurisdictions.....	5
Therapeutics	5
Emergency Use Authorization (EUA) for bamlanivimab	5
WHO guidance development for development and clinical evaluation of monoclonal antibodies.....	6
Research mapping of candidate therapeutics	6
Adverse drug reactions	6
Vaccines.....	7
Announcements of interim analyses from phase 3 studies.....	7
Priority groups for vaccination	7
Living mapping and living systematic review of COVID-19 studies	7
Landscape of candidate vaccines for SARS-CoV-2	7
Research protocols, assays and reference standards.....	8
WHO Working Group: Assays and reference preparations	8
WHO Working Group: Animal models	8
Supply chain.....	9
Substandard and falsified products	9
Medical Devices	10
African Medical Devices Forum’s List of COVID 19 assays, medical devices and PPEs	10

Update on the ACT-Accelerator

Development of WHO living guideline and evaluation timelines for EUL/PQ procedures

An efficient, transparent and trustworthy process has been put into place, and piloted for the corticosteroids, to develop a WHO Living Guideline on Therapeutics and COVID-19. The process includes independent network meta-analysis for each new drug and a standing panel of independent experts to review developments that meets once per week. The target is to publish clinical care guidelines within 3 weeks of availability of data on candidate products. Remdesivir, Lopinavir-Ritonavir, and Hydroxychloroquine guidelines are in process, following the outcome of the Solidarity Trial. A framework has also been built, leveraging WHO Target Product Profiles and ICMRA recommendations, to identify early signals of the need for further discussions with manufacturers of candidate products.

The framework which scores candidate products in areas of efficacy, safety, quality, target populations, programmatic and product complexity, provides a structured and transparent approach for WHO PQ to

22nd WHO Regulatory Update on COVID-19

prioritize early engagement with manufacturers of therapeutic candidates. Work is ongoing by WHO PQ to develop timelines for priority products, to formalize the process for triggering decisions on issuance of Expression of Interests for EUL/PQ, and to specify the differences in data requirement for originators, standalone biotherapeutics, biosimilars and generics.

UNICEF and PAHO joint COVID-19 vaccine tender on behalf of COVAX Facility

UNICEF and the Pan American Health Organization (PAHO) announced, on 12 November, the launch of a tender inviting all COVID-19 vaccine developers to submit a proposal for supply in 2021. The tender, which will run for 6 weeks, aims to provide at least 2 billion doses of COVID-19 vaccines on behalf of the COVAX Facility administered by Gavi, the Vaccine Alliance. The aim of the tender is to ensure equitable and accelerated access to quality assured vaccines for the 186 participating economies as of today.

All manufacturers expecting to have supply available by the end of 2021 at the latest are invited to respond to the tender, including those that have already signed advance purchase commitments with Gavi, as well as those with pre-existing agreements with the Coalition for Epidemic Preparedness Innovations (CEPI) on vaccine development.

[UNICEF news: UNICEF and PAHO launch joint COVID-19 vaccine tender](#) (11 Nov 2020)

COVAX briefing to ICMRA COVID-19 policy group

To promote global regulatory alignment in the evaluation of COVID-19 vaccine candidates, WHO provided a briefing on COVAX, including potential timelines for PQ/EUL decisions and issues that may arise during dossier review, at the 12 November ICMRA COVID-19 Policy meeting. Details of programmatic challenges for one vaccine candidate and WHO working positions on labelling, barcodes and QR codes were shared. The WHO model vaccine roadmap, which includes evaluation of WHO EUL/PQ submissions by a global review committee, and subsequent reliance pathways for in-country regulatory decision making, was also presented. More details will be provided at the next update.

Alignment of approaches by regulators

ICMRA/WHO joint statement

In view of the large number of COVID-19 vaccines and treatments under development, and their potentially imminent roll-out, the WHO and the International Coalition of Medicines Regulatory Authorities (ICMRA) have joined forces to uphold and promote the most rigorous, evidence-based regulatory practices by supporting the alignment of regulatory processes across all countries. To ensure patients have fast access to safe and effective medicines and vaccines, WHO and ICMRA, together with other stakeholders including public health institutions, are committed, as outlined in a joint statement, to a series of actions to help make regulatory alignment happen.

[WHO-ICMRA joint statement: Need for improved global regulatory alignment on COVID-19 medicines and vaccines](#) (06 Nov 2020)

Draft WHO Guidance on Good manufacturing practices for investigational products

In view of an old publication date, and the recent need for new guidelines arising from inspections carried out for COVID-19 therapeutics, the WHO Prequalification Team - Inspection Services (PQT INS) raised the urgency for a revision of the WHO Good manufacturing practices for investigational pharmaceutical products for clinical trials in humans (*Annex 7 WHO Technical Report Series, No. 863*).

The Fifty-fifth Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) concurred

22nd WHO Regulatory Update on COVID-19

with this proposal. The objective of the update is to bring the guideline in line with current expectations and trends in good manufacturing practices and to harmonize the text with the principles from other related international guidelines.

[Draft working document: Good manufacturing practices for investigational products](#)

(for comments by 06 Jan 2021 –[template for comments](#))

Draft WHO Guidance on Good practices for research and development facilities

In view of the recent need for the unprecedented fast development of health products for the treatment of COVID-19 therapies, the WHO PQT INS raised the urgency for the development of good manufacturing practice (GMP) text to address the manufacturing of developmental batches, pilot batches and the sequential stability data that is submitted in product applications (dossiers) for marketing authorization and the prequalification of therapeutic medical products.

There are currently no regulatory guidelines which address this matter, although the data collected from these batches influence the following aspects of the product: stability, process validation, analytical method development and validation.

With an ever-increasing awareness of the risks in pharmaceutical production and control, and the life cycle approaches being followed, more and more emphasis is being placed on ensuring that the research and development of products are appropriately controlled and documented. Furthermore, as regulators request and review data and information such as the development data of products and processes, design of experiments, validation and stability results, it has become necessary to ensure that the facilities, quality systems, data and information meet the appropriate standards and good practices.

[Draft working document: Good practices for research and development facilities](#)

(for comments by 06 Jan 2021 - [template for comments](#))

[Other working documents in publication consultation](#)

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](#).

22nd WHO Regulatory Update on COVID-19

So far, 22 products have been listed as eligible for WHO procurement among 55 expressions of interest for NAT assays, 31 for antibody detection assays and 7 for antigen detection RDTs have been received.

[EUL listed IVDs](#)

[The status of each EUL application](#) (10 Nov 2020)

Implementation project on SARS-CoV-2 Antigen detecting rapid diagnostic test

To monitor implementation of SARS-CoV-2 antigen detecting rapid diagnostic tests (RDTs) in low- and middle-income countries, the WHO Emergencies Department issued an expression of interest to assess:

1. the field performance, feasibility, acceptability and impact of antigen detecting SARS-CoV-2 rapid diagnostic tests in variable use settings in low- and middle-income countries
2. cost and cost-effectiveness of testing strategies using SARS-CoV-2 antigen RDTs in low- and middle-income countries.

This information will be utilized to inform the development of evidence-based policy and implementation guidance.

[SARS-CoV-2 Antigen detecting rapid diagnostic test implementation projects](#)

(deadline for submission is 17 November 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](#) (03 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

Emergency Use Authorization (EUA) for bamlanivimab

The US FDA has issued an EUA for bamlanivimab, a neutralizing IgG1 monoclonal antibody that binds to the receptor binding domain of the spike protein of SARS-CoV-2. It is an investigational drug and is not currently approved for any indication. The EUA is for the treatment of mild-to-moderate COVID-19 in adult and paediatric patients.

Bamlanivimab is authorized for patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kilograms and who are at high risk for progressing to severe COVID-19 and/or hospitalization. This includes those who are 65 years of age or older, or who have certain chronic medical conditions. While the safety and effectiveness of this investigational therapy continues to be evaluated, bamlanivimab was shown in clinical trials to reduce COVID-19-related hospitalization or emergency room visits in patients at high risk for disease progression within 28 days after treatment when compared to placebo.

Bamlanivimab is not authorized for patients who are hospitalized due to COVID-19 or require oxygen therapy due to COVID-19.

WHO guidance development for development and clinical evaluation of monoclonal antibodies

Numerous monoclonal antibodies (mAbs) for treating and preventing infectious diseases are now in development. Because of their relatively short development time, rapid onset of effect and history of safe use, the development of mAbs as potential therapeutics for COVID-19 is a high priority.

Since 2013, a range of WHO guidance documents on mAbs has been published focusing primarily on their use as biotherapeutics for noncommunicable diseases. Comprehensive guidance on the development of mAbs against COVID-19 and other infectious diseases, and on their clinical evaluation, is now urgently needed.

The WHO Expert Committee on Biological Standardization meeting (19-23 October) endorsed a proposal to develop WHO guidance broadly applicable to all mAbs intended for use against infectious diseases, with disease-specific “special considerations” supplements to be drafted as required.

[Executive Summary of the ECBS meeting](#) (5 Nov 2020)

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

International drug safety monitoring is particularly important during global epidemics such as the current COVID-19 pandemic, and even more so when there are no proven vaccines or medicines for the disease. As new COVID-19 vaccines and treatments become available, health-care professionals and patients will need to be actively engaged in monitoring the effects of these novel products and reporting any potential adverse reaction. By analyzing reported reactions, national medicines authorities can take the necessary measures for safer use of the drugs, scientists can assess the data and, if needed, international networks can be activated to address the problem.

WHO promotes global drug safety through its Programme for International Drug Monitoring, which supports countries to develop sound pharmacovigilance policies, organizes hands-on training and workshops, and establishes networks for information sharing. A recent key WHO development is the introduction of a mobile application called “Med Safety”, jointly launched in nine countries¹ with Uppsala Monitoring Centre in Sweden and the UK Medicines and Healthcare products Regulatory Agency. The App enables health-care professionals and patients to report suspected adverse reactions directly to the national authorities’ data base. WHO is preparing to roll out the app in more countries once a COVID-19 vaccine becomes available.

¹ Armenia, Botswana, Burkina Faso, Côte d’Ivoire, Democratic Republic of the Congo, Ethiopia, Ghana, Uganda, Zambia

Vaccines

Announcements of interim analyses from phase 3 studies

On 9 November 2020, Pfizer Inc and BioNTech Se announced their mRNA-based vaccine candidate, BNT162b2, against SARS-CoV-2 demonstrating evidence of efficacy against COVID-19 in participants without prior evidence of SARS-CoV-2 infection, based on the first interim efficacy analysis conducted on November 8, 2020 by an external, independent Data Monitoring Committee (DMC) from the Phase 3 clinical study. The evaluable case count reached 94 and the DMC performed its first analysis on all cases. The case split between vaccinated individuals and those who received the placebo indicates a vaccine efficacy rate above 90%, at 7 days after the second dose. This means that protection is achieved 28 days after the initiation of the vaccination, which consists of a 2-dose schedule. As the study continues, the final vaccine efficacy percentage may vary. The DMC has not reported any serious safety concerns and recommends that the study continue to collect additional safety and efficacy data as planned. The data will be discussed with regulatory authorities worldwide.

Priority groups for vaccination

To support countries in planning, a WHO Strategic Advisory Group of Experts (SAGE) on Immunization published its Roadmap for public health strategies and target priority groups for vaccination for different levels of vaccine availability and epidemiologic settings. The Roadmap will be updated, as necessary, to accommodate the dynamic nature of the pandemic and evolving evidence about vaccine impact.

This is part of a three-step process to provide guidance for overall programme strategy as well as vaccine-specific policy recommendations. The first step was a values framework that outlines the general principles, objectives and related (unranked) target groups for prioritization of COVID-19 vaccines. The second step is the Roadmap. Step 3 is vaccine-specific recommendations.

As market-authorized vaccines become available, specific recommendations for the use of these vaccines will be issued. These recommendations may be updated as additional evidence of effectiveness and safety of market-authorized vaccines (as well as other interventions) becomes available, and as epidemiologic and other contextual conditions evolve.

[WHO SAGE Roadmap for prioritizing uses of COVID-19 vaccines in the context of limited supply](#)
(19 Oct 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

22nd WHO Regulatory Update on COVID-19

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

WHO Working Group: Assays and reference preparations

Studies on the antibody response to SARS CoV-2 were presented at the 4 November meeting. Antibody cloning was used to analyse the antibody response in 6 patients both early (approximately 1 month) and late (approximately 6 months) after infection. Key findings were that memory B cell clonality had evolved over the 6 months period. There was a statistically significant increase in binding affinity to the receptor-binding domain (RBD) of the spike protein and of neutralization potency of IgG antibodies. The driver of this evolution was suggested to be SARS CoV-2 antigen sequestered in the brush-border epithelium of the gut. A number of potent human monoclonal neutralizing antibodies were isolated from the 6 patients. Four different sites of antibody binding on the RBD were identified. Virus escape mutants were generated in vitro to a single monoclonal antibody, but selection of escape mutants was suppressed by using a mixture of monoclonal antibodies covering different binding sites on the RBD. A mixture of two monoclonal antibodies was found to be protective against SARS CoV-2 challenge in hamster and non-human primate models, and to be therapeutic after infection providing the monoclonal antibody mixture was given early after infection.

WHO Working Group: Animal models

5th November meeting:

The development of lung pathology and Clinical Trial (CT) imaging scoring systems for SARS CoV-2 infections in non-human primates (NHP) was described by one group. The scoring systems are being applied to vaccine immunization/challenge trials and also to assessment of candidate therapeutics.

Another group described immunization/challenge results in NHPs with a candidate subunit vaccine based on full-length spike protein from SARS CoV-2. Two doses of vaccine, tested at different doses, protected animals against both disease and against infection, the latter being measured by PCR testing for sub-genomic RNA in nasal turbinates. This finding is being explored further in the hamster model to test whether infection between cage mates is blocked by immunization. The NHP data were used to establish the dose of vaccine that is now being tested in human clinical trials. The developer is also evaluating the durability of the immune response in NHPs. So far, the IgG serum binding response has been shown to be durable for 6 months and will be followed for 1 year. The durability of mucosal immunity is also been evaluated but data are not yet available.

12 November meeting:

A study presented found that some antibodies to SARS CoV-2 enhance infection *in vitro* but not *in vivo*. Five non-neutralizing antibodies were shown to enhance SARS CoV2 pseudovirus infection in 293-ACE2-transfected cells. However, these same antibodies, when studied in an aged mouse model did not enhance weight loss, death, lung haemorrhage score, lung virus titre, or lung subgenomic (sg) RNA when challenged with a mouse-adapted SARS CoV-2 virus. Neither did the same antibodies enhance the lung pathology score, bronchiole lavage or nasal swab sgRNA in young cynomolgus macaques challenged with SARS CoV-2.

Supply chain

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:

- Experimental medicines: remdesivir
- Influenza vaccines

Substandard and falsified products

A WHO Medical product alert was issued on falsified influenza vaccine.

[Falsified Fluzone® Quadrivalent Influenza Vaccine identified in WHO region of the Americas](#) (30 Oct 2020)

Demand on influenza vaccines is high this year as WHO experts have called for health workers and older adults to be considered as the highest priority risk groups to receive influenza vaccines during the COVID-19 pandemic

Various known forces drive the existence of SF medical products. Shortages, unmet or excess demand, and other factors constraining access to specific products should be monitored as this creates a market opportunity for SF versions to penetrate supply chains and reach patients. Covid-19 has diverted attention (and resources) from other health issues and products.

Regulatory authorities should continue to be vigilant for SF versions of Covid19 related therapies, vaccines and in vitro diagnostics and must report these to the WHO Global Surveillance and Monitoring System : rapidalert@who.int.

It is essential to report such products early on, whether suspected or confirmed. Particular vigilance is requested for products which have been the subject of intense media coverage, and products supplied over the Internet.

Medical Devices

African Medical Devices Forum's List of COVID 19 assays, medical devices and PPEs

African Medical Devices Forum (**AMDF**) with the support from the joint secretariat i.e. WHO and AUDA-NEPAD have been developing lists of COVID-19 diagnostic tests and medical devices including PPE which have been listed by WHO PQ/EUL and other regulators. The main objective of this exercise is to facilitate access to listed assays by other jurisdiction and enhance regulatory decision making on these important products for clinical diagnosis of COVID 19, research and epidemiology purposes. These lists have been developed and shared with regulators and other stakeholders in Africa since the early days of the pandemic (April 2020).

To date four lists have been developed and the fifth list is expected to be shared before the end November 2020.

The most recent list endorsed by the African Medicines Regulatory Harmonization (AMRH) Steering Committee is as follows:

[Updated list of COVID-19 IVD tests](#) (Sept 2020)

[Annex 1: COVID-19 NAT listed tests](#)

[Annex 1: COVID-19 Serology listed tests](#)

[Annex 2: list of medical devices and PPEs](#)

Updated lists of registered/authorized/listed medical devices, PPEs and domestic manufacturers of COVID 19 devices and PPEs in Africa will be available in the next update.

Note: AMDF does not endorse any of the lists developed by NRAs but the information is compiled to assist regulators and other stakeholders with ease access to the various lists of COVID 19 assays, medical devices and PPEs.