# Regulation of *in vitro* diagnostics, therapeutics, and vaccines
# WHO Update – 6
# Coronavirus disease 2019 (COVID-19)
# 24 Apr 2020

World Health Organization

**Please do not quote or publish: this update is for internal WHO purposes and for disseminating information to specific stakeholders**

## Key Message

On 24 April, a group of global leaders and health actors launched a landmark, global and time-limited collaboration (termed "COV-ACT") for the accelerated development, production and equitable global access to new COVID-19 essential health technologies. To support this initiative, regulators of the world are called to collaborate, to shorten regulatory review timelines, for example using regional approaches for conducting reviews and other work-sharing and reliance mechanisms. Regulators are also urged to identify and design processes to facilitate rapid regulatory decision making in parallel to clinical development of candidate products.

## Highlights and main issues

- On 24 April, global leaders united launched COV-ACT Accelerator to ensure development, production and equitable access to new COVID-19 diagnostics, therapeutics and vaccines
- WHO listed the fourth Nucleic Acid Test (NAT) assay under the emergency use listing procedure for in vitro diagnostics.
- WHO has held several pre-submission calls with manufacturers of antibody detection rapid tests. Since 17 April such products are eligible for WHO EUL assessments.
- The EMA has published advice to healthcare professionals to closely monitor patients with COVID-19 receiving chloroquine or hydroxychloroquine and to take into account pre-existing heart problems that can make patients more prone to heart rhythm issues.
- WHO continues to receive an increasing number of case safety reports for these and other drugs that are being used to treat COVID-19 patients.
- WHO recommends that countries rapidly ensure that specifications, testing methods and preparedness or capacity of National Quality Control Laboratories (QCLs) for testing of proposed therapeutics for COVID-19 are in place.
- WHO continues to receive numerous notifications of Substandard and Falsified (SF) medical products related to Covid19, in particular chloroquine and hydroxychloroquine and scam/fraud websites that cover a wide range of products, including ventilators.
- A webinar on local production, co-organized by WHO with UNCTAD, was held on 23 April to exchange views and experiences that are critical for sustainable quality-assured local production.

## *In vitro* diagnostics

WHO EUL for SARS-CoV-2 virus IVDs

The WHO Prequalification Team is assessing products for Emergency Use Listing (EUL) for candidate in vitro diagnostics (IVDs) to detect SARS-CoV-2.

On 24 April WHO listed the fourth nucleic acid test (NAT) assay under the emergency use listing procedure for in vitro diagnostics.

> The *PerkinElmer® SARS-CoV-2 Realtime RT-PCR Assay* manufactured by Suzhou Sym-Bio LifeScience Co., Ltd is an in vitro nucleic acid amplification test intended for the qualitative detection of nucleic acid from the SARS-CoV-2 virus in human oropharyngeal swab and nasopharyngeal swab specimens collected from individuals suspected of COVID-19 by their healthcare provider.

A further 25 submissions to WHO are being assessed. At least another 6 submissions are expected.

> Weekly update on applications received is available at:
> www.who.int/diagnostics_laboratory/200421_eul_covid19_ivd_update.pdf?ua=1

As reported previously, antibody detection rapid tests are also eligible for EUL. WHO held several pre-submission calls with manufacturers.

> Instructions for applications are available here.

Information provided by FIND:

> SARS-COV-2: results of molecular assay evaluation
>
> SARS-COV-2: Immunoassays

COVID-19 in vitro diagnostics 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 was published on 21 April. The links can be found at:
> https://www.who.int/diagnostics_laboratory/200420_imdrf_collated_table_20_april_2020.pdf?ua=1
>
> **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

Clinical trials for COVID-19 treatments

Multiple clinical trials of candidate therapeutics are now ongoing worldwide. WHO recommends that these trials should be RCTs, with as large a number of patients as possible.

In addition to these trials, the SOLIDARITY trial, launched by WHO on 18th March is designed to compare, against the standard of care, four treatment options based on evidence from laboratory,

animal and clinical studies: Remdesivir; Lopinavir/ Ritonavir; Lopinavir/Ritonavir with Interferon beta-1a; and Chloroquine or Hydroxychloroquine.

By enrolling patients in multiple countries, the Solidarity trial aims to rapidly discover whether any of the drugs slow disease progression or improve survival.

Compassionate use

WHO is aware that use of candidate therapies is occurring outside of clinical trial settings (compassionate use). WHO cautions that compassionate use without trial provisions, if occurring in multiple sites, is likely to reduce the number of recruits in each clinical trial, thus reducing the power and utility of the study and prolonging the time it will take to understand the benefit-risk profile of each candidate intervention. Compassionate use, if occurring, should therefore also ensure that relevant information is collected to enhance knowledge on the safety and efficacy of these products. WHO therefore recommends patients and healthcare professionals to report any suspected adverse effects to their national regulatory authorities.

Role of therapeutics in prophylaxis and post-exposure prophylaxis

Reports have been published of informal consultations of WHO Therapeutics WG subgroups on (a) post-exposure prophylaxis (PEP) studies and (b) prophylactic (PrEP) studies.

Most prophylaxis study protocols included pre and post- test serological tests. These tests need to be further validated and the WG subgroup proposed that a target product profile for COVID-19 serology is developed. Studies evaluating the validity of self-administered swabs versus the standard practice of physician-administered swabs are also required and are presently being planned.

WHO proposes the development of a core data monitoring committee (DMC), which would have three purposes, to collectively assess safety data and primary endpoints on ongoing PrEP studies and PEP studies (working closely with the DMCs of other studies), and ultimately, this core DMC will be evolved for large core PEP and core PrEP studies.

Landscape of candidate therapeutics for COVID-19

A landscape analysis of candidate COVID-19 therapeutics is regularly published by WHO.

> The analysis is available at:
> https://app.powerbi.com/view?r=eyJrIjoiNjQxZWZhOTItYzU1ZS00Y2QxLWE1ODAtOTViZjhmNjEyZjNiIiwidCI6ImY2MTBjMGI3LWJkMjQtNGIzOS04MTBiLTNkYzI4MGFmYjU5MCIsImMiOjh9

Web-based application to analyse clinical trials to evaluate therapeutics for COVID-19

> The application is available at:
> https://app.powerbi.com/view?r=eyJrIjoiMjA1ZDA0N2YtOTUzMi00ZTU1LWFlMDAtMjFlMTVkN2U2ODQyIiwidCI6ImY2MTBjMGI3LWJkMjQtNGIzOS04MTBiLTNkYzI4MGFmYjU5MCIsImMiOjh9

National Quality Control Laboratory preparedness

WHO recommends that countries rapidly ensure that specifications, testing methods and

preparedness or capacity of National QCLs for testing of proposed therapeutics for COVID-19 are in place. The increased reporting of SFs suggests that countries may need to be prepared to assess quality or have access to testing for the therapeutics including new or re-purposed products. In particular, should re-purposed products like chloroquine and hydroxychloroquine be found to be useful, countries may already have marketing approvals and local capacity to produce that was available long before introduction of ACTs for malaria in the past decade.

However, the dossiers may be old and specifications not compliant with current pharmacopoeia specifications or science. The manufacturers may have stopped production more than a decade ago and may simply want to re-start without appropriate risk assessment and planning for quality and effectiveness. WHO advises regulators to carefully examine predictable risks associated with resumption of production.

Regulators need to be prepared in case there is interest in local production of new products which may result in direct submission of applications for registration without reference to or reliance on a WHO Listed Authority.

Relevant guidelines and product specifications

Information on product specifications is included in the summary list: RELEVANT WHO GUIDANCE FOR SARS-COV2 COVID-19 TREATMENT - MEDICINES

This document is intended to highlight some of the most relevant WHO guidance in the area of pharmaceutical quality assurance and regulatory guidelines for medicines adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations and published in WHO's Technical Report Series (TRS , that may support the development, production, evaluation, distribution and quality control of medicines intended for COVID-19 treatment. This list is prepared following the different product/life-cycle phases and tools provided by WHO.

Monographs on already marketed medicines, which are currently being included in clinical trials to demonstrate their clinical efficacy in treating COVID-19, help to ensure that these medicines meet relevant quality standards. Only the efficacy of quality assured medicines can be compared and evaluated. A list of existing Pharmacopoeial International monographs published by WHO for medicines considered for use in COVID-19 treatment is included in the above-mentioned document.

Moreover, the pharmacopoeias of the world, brought together by WHO under the umbrella of the International Meeting of the World Pharmacopoeias, have started an initiative to view the possibility of developing harmonized quality standards on active pharmaceutical ingredients and finished pharmaceutical products that may potentially be used in the treatment of COVID-19 and for which no specifications exist. Harmonized quality standards will facilitate the development, regulatory assessment, distribution and post-marketing surveillance of these medicines.

Traditional Chinese Medicines (TCMs)

Three TCMs have had indications extended to include COVID-19 by the National Medical Products Administration, China. The three TCMs were originally developed and used for:

i. Jinhua Qinggan Granule – developed during the flu H1N1 pandemic in 2009 and has efficacy similar as Tamiflu, but with less adverse effects and lower cost.
ii. Lianhua Qingwen Capsule - developed to treat viral infections during the SARS epidemic in 2003
iii. Xuebijing Injection- TCM injection of a multi-targeted drug, found effective in the early study of severe pneumonia and sepsis

Further information is available at: http://subsites.chinadaily.com.cn/nmpa/NMPA.html,
**Note: WHO does not endorse any of these products. The information is provided exclusively to assist stakeholders with identifying the links to the products.**

Validity of e-certificates (eCPPs)

Since 30 March EMA has started to issue electronic CPP certificates and, although, most countries have accepted this development some countries have expressed concerns about the authentication of the validity of the certificates. To address this problem EMA has issued an explanatory note. The new explanatory document on format, safety features and the Agency´s measures to support confirmation on the validity of electronic certificates has been published in EMA website.

The links are at:

EMA eCertificates during the COVID-19 pandemic
EMA Information note on the format and validity features of eCertificates

## ADR reporting and mitigation measures for drugs used for COVID 19 Management

COVID19 Solidarity Trials: Pharmacovigilance update

A total of 255 reports were extracted, with the search-term coronavirus-infection, from Vigibase, the WHO global database of individual case safety reports. The reports were received at the National Pharmacovigilance Centres between 1 January and 12 April 2020 and were reported to VigiBase no later than 12 April 2020.

Reports came from 15 countries, representing three WHO regions: Europe (246 cases), the Americas (7 cases) and the Western Pacific (2 cases). 58% (149) of the reports were classified as "serious". The age of the patients in the reports ranged between 5 days and 95 years. 66% (169) of the reports were in males, 32% (80 reports) in females, with no information on the sex of patients in the remaining reports. Most of the reports included at least one of the SOLIDARITY trial drugs.

The search also identified additional reports describing other drugs being used in the treatment of COVID-19 disease, such as tocilizumab (10 reports) and oseltamivir (4 reports). The reported adverse events are largely in line with those expected according to product labelling and/or other sources of drug information.

A descriptive analysis of the case reports is available at this link:
https://www.who.int/medicines/regulation/medicines-safety/ICSRs-COVID19-April-12.pdf?ua=1

Reminder of serious side effects with chloroquine and hydrochloroquine

Chloroquine and hydroxychloroquine are known to potentially cause heart rhythm problems, and these could be exacerbated if treatment is combined with other medicines, such as the antibiotic azithromycin, that have similar effects on the heart. Recent studies carried out in patients with coronavirus disease (COVID-19) have reported serious, in some cases fatal, heart rhythm problems with chloroquine or hydroxychloroquine, particularly when taken at high doses or in combination with the antibiotic azithromycin.

The EMA has published advice to healthcare professionals to closely monitor patients with COVID-19 receiving chloroquine or hydroxychloroquine and to take into account pre-existing heart problems that can make patients more prone to heart rhythm issues. They should carefully consider the possibility of side effects, particularly with higher doses, and exercise extra caution when combining treatment with other medicines such as azithromycin that may cause similar side effects on the heart. Patients and healthcare professionals are reminded to report any suspected side effects to their national regulatory authorities.

The document is at: www.ema.europa.eu/en/news/covid-19-reminder-risk-serious-side-effects-chloroquine-hydroxychloroquine

## Vaccines

SOLIDARITY clinical trial protocol for candidate SARS-CoV-2 vaccines.

An updated study synopsis has been published, providing more details of the protocol. Regional regulatory review of the protocol is encouraged and WHO will work with networks to facilitate this process.

Updated synopsis

ToRs and memberships of the following WHO vaccines WGs have been posted:

- *Vaccine Target Product Profile*
- *Vaccine prioritization*
- *Vaccine R&D*
- *Vaccine Core Protocol*

Landscape of candidate vaccines for SARS-CoV-2

A landscape analysis of candidate SARS-CoV-2 vaccines is regularly published by WHO. So far 6 candidate vaccines are in early-stage clinical trials and a 7th is expected to start next week. This illustrate an unprecedented acceleration of progress with potential candidates.

The 23 April 2020 version is available at: www.who.int/blueprint/priority-diseases/key-action/draft-landscape-COVID-19-candidate-vaccines-23-April-2020.pdf?ua=1

Standards for calibration of serological assays for SARS-CoV-2

Serological assays are needed to understand the real impact of COVID-19, as most of the cases with mild symptoms are undetected. Urgent and rapid vaccine development is underway; currently there are more than 70 vaccine candidates and 6 vaccines have entered phase I clinical trials. The scientific and clinical community requires a SARS-CoV-2 antibody standard urgently for serological assay development, evaluation of vaccine efficacy, and for epidemiological studies. Plasma or serum from convalescent patients is the preferred candidate standard as these are commutable, due to most closely representing clinical samples that are analysed in the assay. These samples have

consistently been able to reduce inter-assay variability when used as a calibrant for a range of tests, as shown for many other viruses, including MERS-CoV.

The WHO collaborating center for biological standardization, the National Institute for Biological Standards and Control (NIBSC), UK, is leading projects with the support of other WHO collaborating centers and worldwide laboratories to develop appropriate reference materials. Donors have been identified from affected countries (UK, Norway, Italy, USA, Singapore) and the first research reagents are anticipated to be available for issue at the end of April.

Further details are at: https://www.who.int/biologicals/Standardization_Covid-19/en/.

## Enabling research; animal models, clinical trial protocols, assay development, standards

WHO Working Group on Assays and Reference Preparations

The April 22 meeting of the WG was devoted to discussion of surrogate virus neutralization tests. These are competitive ELISAs based on blocking of binding of soluble RBD to hACE coated plates by serum from patients. At least one assay of this design is being commercialized with plans to submit for NRA evaluation. The WG were enthusiastic about the potential of such assays, which if validated against virus neutralization tests, will simply assay of this key marker of immunity.

The WG are collating information on assay comparison studies that are underway. In addition to the ongoing study by FIND, which is expected to continue through May and June, the University of Colorado, USA and PATH, Seattle, USA have started studies. Other groups were invited to inform the WG of additional studies.

NIBSC have completed in-house characterization of a candidate SARS-CoV-2 antibody research reagent and will fill 2000 vials next week, and plan to make these available the following week. NIBSC are also preparing 500 antibody panels consisting of 5 preparations with differing ant-SARS-CoV-2 contents.

WHO Working Group on Animal Models

The Working Group meeting on 23 April were updated on progress with two purified whole virus inactivated alum adjuvanted vaccines. Pre-clinical data, including immunization/challenge experiments in monkeys, were briefly described. It was also reported that, after review of the pre-clinical data by the NRA, both of the vaccines have entered phase 1 clinical trials in China.

## Blood supply and use of blood components

Convalescent plasma trials

The current situation where vaccines or therapeutics effective for COVID-19 are not yet available has prompted several countries to use convalescent plasma (CP) for treatment either in clinical trials or in

compassionate use. WHO is committed to liaise with its international partners to obtain and share information on countries conducting studies on CP. Position statements and/or study protocols for evaluation of CP have been issued by a number of Member States and are listed in the table. **WHO does not endorse any of the statements or protocols. The information is provided exclusively to assist stakeholders with identifying the links to the various statements and protocols.**

| INITIATOR | TITLE OF DOCUMENT | LINK TO THE DOCUMENT |
|---|---|---|
| Saudi Arabia,<br>King Abdulaziz University Jeddah | Use of Convalescence Plasma in The Treatment of Patients Infected with Covid-19 Virus Infection Protocol Version V 1.2 | isbtweb.org/coronaoutbreak/convalescent-plasma-covid-19-resources/ |
| SIMTI (Societa Italiana di Medicina Transfusionale e Imunoematologia)<br>SIdEM (Societa Italiana di Emaferesi e Manipulazione Cellulare) | Convalescent Plasma "Position paper" on the preparation of immune plasma to be used in the treatment of patients with COVID-19 | isbtweb.org/coronaoutbreak/convalescent-plasma-covid-19-resources/ |
| US FDA | • National initiative to provide COVID-19 Convalescent Plasma for use in controlled trials<br>• Expanded access to Convalescent Plasma for the Treatment of Patients with COVID-19<br>• National COVID-19 Convalescent Plasma Project | • www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-coordinates-national-effort-develop-blood-related-therapies-covid-19.<br>• www.uscovidplasma.org.<br>• https://ccpp19.org/ |
| UP-Philippine General Hospital Technical Working Group on Convalescent Plasma Therapy | Guide on The Compassionate Use of Convalescent Plasma Therapy for Covid-19 | isbtweb.org/coronaoutbreak/convalescent-plasma-covid-19-resources/ |
| European Commission Directorate-General for Health and Food Safety Directorate B - Health systems, medical products and innovation | An EU programme of COVID-19 convalescent plasma collection and transfusion Guidance on collection, testing, processing, storage, distribution and monitored use | ec.europa.eu/health/blood_tissues_organs/covid-19_en |
| ISBT Working Party on Global Blood Safety | Points to consider in the preparation and transfusion of COVID-19 convalescent plasma | isbtweb.org/coronaoutbreak/convalescent-plasma-covid-19-resources/ |
| U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research | Investigational COVID-19 Convalescent Plasma Guidance for Industry | isbtweb.org/coronaoutbreak/convalescent-plasma-covid-19-resources |
| Pan American Health Organization (PAHO) | Consideraciones regulatorias sobre la autorización del uso de plasma de convalecientes (PC) para atender la emergencia de COVID-19 | https://iris.paho.org/handle/10665.2/52024 |

## Falsified and substandard products

WHO continues to receive numerous notifications of SF medical products related to Covid19, in particular chloroquine and hydroxychloroquine and scam/fraud websites that cover a wide range of products, including ventilators. Any suspected or confirmed falsified/substandard medical products (including IVDs or other medical devices for COVID-19) should be reported to rapidalert@who.int

A WHO Information Notice for Users (available in English, French, Spanish) destined to end-users and other supply chain actors encourages due diligence in procurement of IVDs and give guidance on how to identify suspect products. Link: https://www.who.int/diagnostics_laboratory/procurement/complaints/en/ .

WHO is working on developing "targeted surveillance lists" which will be disseminated to the network of official regulatory focal points. This list will cover SF products likely to be circulating in one or more regions and for which increased regulatory vigilance is requested, including products affected by current Covid19 crisis.

## Supply chain

Issues noted from WHO Regional Offices

Stakeholders in countries are requesting guidance documents on the use, availability and status of medicines used in the response to COVID-19. The landscape of regulatory, use and availability of medicines in scarce supply is a complex environment, particularly for audiences that may not be familiar with intersection of regulatory affairs and procurement. Guidance has been developed and provided to national stakeholders in some regions, addressing issues such as the procurement of medicines that are currently in clinical trials. While evidence is still being collected from trials, there is also confusion regarding the number of countries that have already provided emergency use listings. In these cases in particular, this opens issues for competing demands for normal programmatic use of certain medicines, including, but not limited to chloroquine, hydroxychloroquine, and lopinavir/ritonavir.

Donation initiatives

Donation programs have emerged through bi-lateral initiatives, notably an initiative from the Government of Japan who has offered to donate Favipiravir to a number of countries. While WHO is not implicated in this programme, the available information suggests that bi-lateral discussions regarding market authorizations, pharmacovigilance and other issues are ongoing between the sponsor and participating countries.

Consolidation of UN procurement

WHO coordinates a group of UN partners, including multiple subgroups that are distributing PPE and other supplies. Major shipments of PPEs have been made, and more are scheduled in weeks to come. The World Food Programme, which is a member of the UN collaboration, is identifying transportation options for countries that are particularly vulnerable to the transportation and market slowdowns. Shortages and insufficient manufacturing capacity are impacting the supply of products, including oxygen equipment, some PPEs and others.

Transportation

Transportation remains a critical problem and is linked to increasing shortages in some countries. The problem of limited flight availability as well as intra-country transportation have been cited by

multiple countries. Two countries have started collaborations with major carries to repurpose some passenger flights to carry cargo, but more action will be needed to assure that flights, warehouse staff and transportation staff are able to safely return to work in affected countries and sub-national regions. See the note on deliveries by the World Food Programme above.

Manufacturing capacity

While manufacturing capacity in China is reported to have normalized, not all companies have recovered completely.

The confinement measures in India continue to impact access to factories, warehouses and transportation services. Industry associations report that while their inventories and current production will be able to meet current demands and commitments, they are dependent on support in managing critical workers and transportation issues. The WHO Country Office in India is engaged with in supporting various high-level working groups across Ministries within the Government of India to identify solutions.

Export restrictions

There are daily changes to export restrictions, which are contributing to the challenges of transportation and shortages. As some restrictions have been lifted (e.g., India), others have been initiated (e.g., Turkey).

A high-level message from WHO Director General Tedros and WTO Director General Roberto Azevêdo have called countries to action to improve solidarity and reduce chaotic impact of the export restrictions. www.who.int/news-room/detail/20-04-2020-joint-statement-by-wto-director-general-roberto-azev%C3%AAdo-and-who-director-general-tedros-adhanom-ghebreyesus.

On practical aspects of implementation, WHO has released a letter to address customs bottlenecks for humanitarian cargo and will continue to monitor and respond to other implementation issues in this area.

Procurement of medicines for off-label use

WHO and partners are receiving increasing requests to procurement medicines that include some of the repurposed medicines currently in clinical trials. While evidence is yet inconclusive regarding the use of the repurposed medicines, some countries' national medicines regulatory authorities have approved their use in treatment of COVID patients. WHO will continue to respond to requests for these medicines in three circumstances: for use as indicated (for existing "repurposed" medicines); for use according to other indications approved by a national medicines regulatory authority, including management of COVID-19 (where applicable); and in the case of medicines for use in clinical trials, some products in the Solidarity Trials may be available for trial sites.

Technical specifications and local production

A webinar on local production was recently conducted to address questions related to local manufacturing of PPEs. Some countries have significant manufacturing capacity that can be repurposed to make PPEs, but not all countries have local capacity and require additional

assistance with specifications, quality standards and the means to perform adequate quality control and quality assurance.

Aa second related webinar, co-organized by WHO with UNCTAD, was held on 23 April to exchange views and experiences that are critical for sustainable quality-assured local production. Roundtable discussions focused on production capacities of therapeutics, challenges in relying on active pharmaceutical ingredients produced abroad, ensured market demand, importance of strengthening regulatory systems with increased efficiency and flexibility.

Shortages

Shortages of specific products continue. There are a number of factors impacting medicine supply in countries of all income levels. WHO is working with industry associations and regulators for solutions wherever possible. The main factors, which compound on each other, include the following, plus others:

- Panic and speculative procurement of medicines in clinical trials;
- Increased freight costs, in some cases reaching 1000%;
- Spikes in demand for specific medicines, especially for certain ICU medicines;
- Medicines using the same primary ingredients as those moving into high demand;
- Export restrictions, which are starting to ease in some areas;
- Production slowdowns related to quarantine measures and inability to obtain materials;
- Limited transportation, including inter-country and intra-country transport, affecting exports of medicines.

A partial list of medicines reported to be in shortage include the following:

- Antibiotics (azithromycin, levofloxacin, metronidazole)
- ICU medicines (in general: anaesthsia, sedatives, muscle relaxants, and renal replacement fluids; specific products: fentanyl, paracetamol, epinephrine and norepinephrine, Propofol and antibiotics as above)
- Palliative care medicines (morphine)
- Malaria treatments (hydroxychloroquine, chloroquine, Artemether-lumafantrine, Artemisinin-based combination therapies, Sulfadoxine-pyrimethamine + amodiaquine).
- HIV: Lopinavir/ritonavir

Regulators and procurers are working together to find solutions to these problems on a country by country basis, including:

- alternative supply sources and the regulatory flexibilities to facilitate the implementation;
- global labeling to facilitate broader releases to markets
- shifting patients to alternative therapies (in the case of lopinavir/ritonavir)

WHO continues to monitor shortages across regional networks, industry associations and regulatory networks.

# Medical Devices

Information on medical devices, including PPE, oxygen supply systems and medical equipment can be found in the COVID site: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/covid-19-critical-items

## Oxygen sources and distribution for COVID-19 treatment centres

This interim guidance, adapted from WHO and UNICEF's technical specifications, is intended for health facility administrators, clinical decision-makers, procurement officers, planning officers, biomedical engineers, infrastructure engineers and policy-makers. It describes how to quantify oxygen demand, identify oxygen sources that are available, and select appropriate surge sources to best respond to COVID-19 patients' needs, especially in low-and-middle income countries.

www.who.int/publications-detail/oxygen-sources-and-distribution-for-covid-19-treatment-centres

## List of Priority Medical Devices for COVID-19 Case Management

This list presents the different types of medical devices including medical equipment, personal protective equipment (PPE), and other medical supplies for the management of COVID-19 patients (not in priority order). It also describes alternative options that should be considered based on available infrastructure, health workforce and technologies. Please note some are capital equipment that requires accessories, spare part and extended warranties.

– Control+click here to access the document

## Emergency global supply chain system catalogue

This catalogue lists all the medical devices including personal protective equipment, medical equipment, medical consumables, single use devices and laboratory and test related devices.

www.who.int/docs/default-source/coronaviruse/20200412-catalogue-v9.pdf?sfvrsn=ddd851d5_2

## Forecasting supplies, diagnostics and equipment requirements

The WHO COVID-19 Essential Supplies Forecasting Tool (ESFT) is designed to help governments, partners, and other stakeholders to estimate potential requirements for essential supplies to respond to the current pandemic of COVID-19. Although it provides an estimation of the number of cases, this calculator is not an epidemiological calculator. The focus of this tool is to forecast essential supplies: it includes estimation of personal protective equipment, diagnostic equipment, biomedical equipment for case management, essential drugs for supportive care, and consumable medical supplies.

- Control+click here to access the forecasting tool

- FAQs: WHO COVID-19 Essential Supplies Forecasting Tool (COVID-19 ESFT)

## African Medical Devices Forum (AMDF) COVID-19 Task Force

African Medical Devices COVID-19 Task Force with the technical guidance from WHO continued with meetings and the following are the latest outputs:

1. A list of Nucleic Acid tests (NAT) which have been authorized for Emergency Use to establish diagnosis of COVID-19 infection has been updated to include newly listed tests by WHO Prequalification and United States Food and Drug Administration (US FDA).
2. A list of COVID-19 serology assays which have been authorized for Emergency Use by United States Food and Drug Administration (US FDA), Health Canada, Therapeutic Goods Administration (TGA), Singapore Food and Drug Administration and Nigeria Agency for Food and Drug Administration (NAFDAC). The list has clearly stated that "WHO does not recommend use of serology assays to establish diagnosis of COVID-19 infection"
3. A list of medical devices and personal protective equipment (PPEs) has also been updated to include medical devices which have been authorized by Saudi Food and Drug Authority (SFDA).
4. Standard operating procedure for handling complaints for substandard and falsified medical devices including in vitro diagnostic tests was updated.
5. Guidance on assessment of donations of medical devices including in vitro diagnostic tests for in country use during emergencies has been updated to include the role of the National Procurement Agents.

Previous documents that were developed by the AMDF Task Force have been shared with the National Regulatory Authorities, REC Secretariats and other key partners and have been uploaded on the WHO AMDF MedNet Platform.

## Sharing information by regional regulatory groups

PAHO/WHO and the Pan American Network for Drug Regulatory Harmonization (PANDRA)

A network of regulatory focal points to respond to the COVID-19 pandemic in a rapid and coordinated way have been established by PAHO/WHO. Bi-weekly meetings are hosted in two languages (English and Spanish) to discuss updates on regulatory responses and to address regulatory challenges and concerns. Two meetings were already arranged, and the third meeting will be on 23 April 2020, to discuss the applicability of Reliance for Emergency Use Authorization of Medicines and Other Health Technologies in a Pandemic (e.g. COVID-19).

This initiative is key for PAHO/WHO to identify areas where immediate support is needed, to better plan any response needed. WHO HQ has actively supported this effort by weekly providing/sharing regulatory updates, facilitating the communication platform, and attending the above-mentioned meetings.

Moreover, as the Pan American Network for Drug Regulatory Harmonization (PANDRH) Secretariat, PAHO has been regularly sharing information, in both Spanish and English, on COVID-19 regulatory actions in the Region available at the public level. Such actions are mainly focused on authorization of medicines and other health technologies under an emergency situation, supply of medicines and medical devices, regulatory flexibilities in on registration or import of critical products, as well as warnings of fraudulent products and potential blood shortages during the COVID-19 pandemic, among others.

For further information on PANDRH's initiative, please send a message to cparf@paho.org

The African Vaccines Regulatory Forum (AVAREF) to expedite COVID-19 clinical trial reviews

National regulatory authorities and national ethics committees from across Africa have agreed to combine their expertise to expedite clinical trial review and approvals for new multinational preventive, diagnostic and therapeutic interventions to the COVID-19 pandemic. Joint reviews are based on voluntary cooperation between the relevant national regulatory authorities and ethics committees. Each country remains solely responsible for granting regulatory approval.

The agreement was reached during a virtual meeting convened by WHO on 1 April 2020 under the platform of the AVAREF, one of the Continental Technical Committees of the African Medicines Regulatory Harmonization Initiative. The approach to be used by AVAREF has already been successfully applied to important vaccines against meningitis, malaria, rotavirus, pneumococcal pneumonia and Ebola and has been extended to other therapeutic interventions.

The Member States of AVAREF agreed to adopt measures, given below, to address the challenge to expedite COVID-19 clinical trial reviews:

- An online platform (SharePoint) will be made available for joint reviews of clinical trial applications for preventive, diagnostic and therapeutic interventions related to the COVID-19 pandemic. Participating countries (national regulatory authorities, national ethics committees and targeted ethics review boards) will post their queries online for real-time response from sponsors/applicants
- The secretariat of the AVAREF will convene and coordinate virtual meetings for participating countries to conduct joint reviews of clinical trial applications on COVID-19
- Virtual meetings will also be used to discuss pertinent issues on how regulators and ethics committees can better prepare and respond to the COVID-19 pandemic
- Regulatory authorities and ethics committees can use a separate platform (MedNet) to share information on planned or ongoing clinical trials in their countries
- A timeline of 10 working days is suggested for processing of clinical trial applications via the joint review pathway where the product is already registered for other indications, and 15 working days for novel products

For more information please contact Diadié Maiga at maigad@who.int or Dicky AKANMORI akanmorib@who.int

Weblinks:

www.afro.who.int/health-topics/immunization/avaref

www.nepad.org/news/african-regulatory-agencies-ethics-committees-expedite-covid-19-clinical-trial-reviews

## Regulatory Flexibility initiatives

In order to mitigate the risks of shortages and stockouts, a number of regulators have produced temporary guidance on regulatory flexibility. Some examples are included below. WHO is working with international regulators to develop best practices.

| | | |
|---|---|---|
| EU | Regulatory flexibility guidance | ec.europa.eu/health/sites/health/files/human-use/docs/guidance_regulatory_covid19_en.pdf |
| US FDA | Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency | www.fda.gov/media/136238/download |
| US FDA | Postmarketing Adverse Event Reporting for Medical Products and Dietary Supplements During a Pandemic | www.fda.gov/media/72498/download |
| US FDA | Permanent Discontinuance or Interruption in Manufacturing Under Section 506C of the FD&C Act | www.fda.gov/media/136486/download |
| UK MHRA | Exceptional good distribution practice (GDP) flexibilities for medicines during the coronavirus (COVID-19) outbreak | www.gov.uk/guidance/exceptional-good-distribution-practice-gdp-flexibilities-for-medicines-during-the-coronavirus-covid-19-outbreak |
| UK MHRA | Exceptional GMP flexibilities for medicines imported from third countries during the coronavirus (COVID-19) outbreak | www.gov.uk/guidance/exceptional-gmp-flexibilities-for-medicines-imported-from-third-countries-during-the-coronavirus-covid-19-outbreak |
| UK MHRA | MHRA regulatory flexibilities resulting from coronavirus (COVID-19) – covering: Blood components for transfusion; Clinical trials; Inspections and good practice; Medical Devices; Medicines regulation; Pharmacovigilance. | www.gov.uk/guidance/mhra-regulatory-flexibilities-resulting-from-coronavirus-covid-19 |
| CA HC | Exceptional Access to Drugs | www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/covid19-interim-order-drugs-medical-devices-special-foods/information-provisions-related-drugs-biocides.html |
| CA HC | Diagnostic Devices | www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/covid-19.html |
| CA HC | Hard Surface Disinfectants and Hand Sanitizers | www.canada.ca/en/health-canada/services/drugs-health-products/disinfectants/covid-19.html |
| CA HC | Exceptional Access to Medical Devices | www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/covid19-interim-order-drugs-medical-devices-special-foods/medical-device-exceptional-import.html |
| AU TGA | TGA response to coronavirus (COVID-19) – covering: Medicine shortages; Access to coronavirus tests, medicines and vaccines; Advertising of products; GMP information for sponsors and manufacturers; | www.tga.gov.au/media-release/tga-response-coronavirus-covid-19 |
| AU TGA | Post market review of COVID-19 point-of-care tests | www.tga.gov.au/post-market-review-covid-19-point-care-tests |
| AU TGA | Exemption for coronavirus (COVID-19) medical devices | www.tga.gov.au/exemption-coronavirus-covid-19-medical-devices |
| AU TGA | COVID-19 limits on dispensing and sales at pharmacies | www.tga.gov.au/media-release/covid-19-limits-dispensing-and-sales-pharmacies |
| AU TGA | Expedited COVID-19 medical device application process | www.tga.gov.au/expedited-covid-19-medical-device-application-process |
| JP PMDA | Handling on regulatory reviews of drugs, medical devices, IVDs, and regenerative medical products for the time being associated with COVID-19 (Administrative Notice dated April 13, 2020) | www.mhlw.go.jp/hourei/doc/tsuchi/T200415I0010.pdf |

| | | |
|---|---|---|
| | → The notice writes that medical products related to COVID-19 are subject to priority review. | |
| JP PMDA | Handling on clinical trial notifications of COVID-19 (Administrative Notice dated March 19, 2020)<br>→ The notice permits that clinical trials on COVID-19 can be started without waiting 30 days after the submission of clinical trial notification if investigation by PMDA is completed | www.mhlw.go.jp/hourei/doc/tsuchi/T200323I0040.pdf |
| JP PMDA | Handling on the storage of informed consent forms during clinical trials (Administrative Notice dated April 7, 2020)<br>→ The notice permits that alternative method can be used when signed informed consent forms are difficult to be stored because of infection etc. in clinical trials for patients with infectious disease. | www.mhlw.go.jp/hourei/doc/tsuchi/T200408I0010.pdf |
| JP PMDA | Handling on adverse drug reaction reports of medical products in dealing with COVID-19 (Administrative Notice dated March 9, 2020)<br>→ The notice permits that adverse drug reaction reports can be simplified (including omission of seal) during COVID-19 pandemic. | www.pmda.go.jp/files/000234755.pdf |
| JP PMDA | Q&A on clinical trial of drugs, medical devices, and regenerative medical products under the influence of COVID-19<br>→ The notice permits flexibility in handling investigational products and having IRB. | www.pmda.go.jp/files/000234815.pdf |
| SP EMPS | Guidance on exceptional measures on clinical trials and observational studies to handle problems arising from COVID-19 emergency.<br>- Dedicated webpage with the repository of guidance and updates regarding COVID19 | www.aemps.gob.es/la-aemps/ultima-informacion-de-la-aemps-acerca-del-covid%E2%80%9119/ |
| IN CDSCO | Circular regarding procedure for lot release of Human vaccine in view of prevailing COVID-19 pandemic | https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=NTgxNg |

## Access to regulatory updates by WHO staff

All WHO staff have access to the Regulatory Updates at the following location:
P:\PubPersons\RPQ\COVID_Regulatory_Updates