Regulation of *in vitro* diagnostics, therapeutics, and vaccines
WHO Update – 2
Coronavirus disease 2019 (COVID-19)
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World Health Organization

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Key Messages

Regulators have a critical role to inform decision makers that consideration of a candidate therapeutic by WHO does NOT mean that it works. In fact, it means we are not at all sure, and need to test it very carefully, otherwise the product being tested could do no good and could actually do harm. WHO has issued a statement on off-label and compassionate use of pharmaceutical products for COVID-19.

WHO has received at least 20 reports of suspected falsified diagnostics, medicines, and vaccines, all related to Covid19. Due diligence is required from all in the procurement, use and administration of medical products, in particular those affected by the current crises or related to Covid19.

Highlights and main issues

- The African Vaccine Regulators Forum (AVAREF) has agreed to organize joint reviews including in-country joint reviews between NRAs and ECs of the Solidarity Protocol. Other regulatory networks in different regions are encouraged to consider doing so too.
- Animal infection models are now being used to study potential treatments.
- WHO publishes interim guidance on the management of the blood supply in response to the COVID-19 pandemic.
- WHO publishes guidance on off-label use
- WHO agrees with an initiative to use e-signature for the certificates issued in the context of WHO Certification scheme on the quality of pharmaceutical products moving in international commerce.

In vitro diagnostics

COVID-19 in vitro diagnostics listed by National Regulatory Authorities in IMDRF jurisdictions

8 countries (Australia, Brazil, Canada, China, Russia, Singapore, South Korea, USA) have listed IVDs for diagnosis of COVID-19 on the basis of expedited regulatory assessments. To help other countries, WHO published links to these emergency lists, together with contact details. The links provided present information on IVDs authorized for use in the International Medical Device Regulators Forum (IMDRF) jurisdictions along with other useful information on policies and guidance. **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.** WHO will provide updated versions as new information becomes available.

The links can be found at:
https://www.who.int/diagnostics_laboratory/200325_imdrf_covid19_listing_update_25_march_2020.pdf?ua=1

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. Currently, assays for the detection of SARS-CoV-2 nucleic acid are eligible for EUL assessment. Information on applications received, which is updated weekly, is summarized below and can be found at:
Update on 24 March 2020

Summary table: 24 March 2020

Product type: NAT		
Stage of process	QMS review	Documentary evidence review
In process	8	10
In process and additional information requested from manufacturer	2	0
Total EUL applications screened or reviewed	10	10
Awaiting submission	6	6

Laboratory testing strategy recommendations for COVID-19

There is much current interest in the role of serology and point of care tests for SARS-CoV-2. WHO issued interim guidance on laboratory testing on 22 March, available at the link below. The guidance states that serological assays will play an important role in research and surveillance but are not currently recommended for case detection. The role of rapid disposable tests for antigen detection for COVID-19 needs to be evaluated and is not currently recommended for clinical diagnosis pending more evidence on test performance and operational utility. WHO will update this guidance as more information on laboratory tests for COVID-19 becomes available. Based on this guidance, serology assays are not including in the EUL scope. However, the EUL scope will be quickly adjusted if this guidance changes.
https://apps.who.int/iris/bitstream/handle/10665/331509/WHO-COVID-19-lab_testing-2020.1-eng.pdf

Therapeutics

Off-label and compassionate use of candidate therapeutics

An unintended consequence of the identification by WHO of candidate therapeutics for clinical evaluation has been stock-outs of these drugs. As some are re-purposed drugs with existing indications it is making it difficult in some instances for patients to access their ongoing treatments. Also, widespread compassionate use of the candidates, whilst understandable in the heat of a crisis, is making it difficult to recruit into a randomized placebo-controlled trial. It is very important, and regulators have a critical role, to inform decision makers that consideration of a candidate therapeutic by WHO does NOT mean that it works. In fact, it means we are not at all sure, and need to test it very carefully, otherwise the product being tested could actually do harm.
For example, in a trial of a candidate identified by WHO, Lopinavir–Ritonavir, no benefit was observed in hospitalized adult patients with severe Covid-19 beyond standard care. Future trials in patients with severe illness may help to confirm or exclude the possibility of a treatment benefit.
See: Cao et al, A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. DOI: 10.1056/NEJMoa2001282

To assist decision makers, WHO have issued a statement on off-label and compassionate use of pharmaceutical products for COVID-19.
https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen

Solidarity trial

AVAREF has agreed to organize joint reviews including in-country joint reviews between NRAs and ECs. Other regulatory networks are encouraged to consider doing so to.
So far, close to 40 countries have expressed an interest in engaging on the Solidarity Trials announced by the DG on the 18th of March. If there are new requests for engagement, please forward the offers to Patrick Lydon, lydonp@who.int , cc Marie Pierre Preziosi, preziosim@who.int, Ana Maria Henao-Restrepo, henaorestrepoa@who.int, and David Wood, woodd@who.int .

Vaccines

Accelerated development timelines for SARS- CoV-2 vaccine candidates

The report of a TC of regulators convened on March 18, by the International Coalition of Medicines Regulatory Authorities (ICMRA), and co-chaired jointly by EMA and FDA, has been published. The rapid spread of SARS-CoV-2 requires accelerated development timelines for SARS- CoV-2 vaccine candidates. The type and extent of preclinical and preliminary clinical data needed to inform the clinical development program for SARS-CoV-2 vaccines must be weighed against the overall risk-benefit assessment of the unmet medical need for vaccines to confront this challenge. Key topics discussed were:

- Preclinical data required to support proceeding to First in human clinical trials
- The need to address the theoretical risk for SARS-CoV-2 vaccine-induced disease enhancement prior to proceeding to FIH clinical trials

The report, available at the link below, represents generally agreed positions among global regulators in attendance.
http://www.icmra.info/drupal/sites/default/files/2020-03/First%20regulatory%20COVID-19%20workshop%20-%20meeting%20report_March%202020.pdf

Candidate vaccines

As of 21 March, 2 candidate vaccines against SARS-CoV-2 were in phase 1 trials and 48 others, many using novel vaccine technologies, are in pre-clinical development. Details of the vaccine candidates are given in the link from the WHO R&D group;
https://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus-landscape-ncov-21march2020.PDF?ua=1

A summary of the platforms being used is as follows;

Stage of vaccine development	Type of platform	Number of vaccine candidates	
Phase 1 clinical	Non-replicating viral vector	1	Ad 5 vector; trial in China
	RNA	1	LNP-encapsulated mRNA; trial in USA
Pre-clinical	DNA	3	
	Inactivated whole virus	1	Alum adjuvanted
	Live attenuated	1	
	Non-replicating viral vector	6	5 adeno-based vectors; 1 vaccinia vector
	Protein subunit	17	8 spike protein; 9 other targets

	Replicating viral vector	5	2 measles vectors; 1 horsepox; 1 influenza; 1 VSV
	RNA	7	4 mRNA; 2 LNP-encapsulated mRNA; 1 saRNA
	VLP	1	Plant-derived
	Unknown	7	

Blood supply and use of blood components in the response to COVID-19

The COVID-19 virus outbreak is primarily transmitted by the respiratory route and theoretically by transfusions. The risk of transmission of COVID-19 through transfusion of blood and components is likely minimal.

The epidemic has the real potential however to reduce the supply of blood and blood components and adversely affect blood system activities Experience with outbreaks of other coronaviruses suggests that there will be significant impact. Blood services should therefore take steps to assess, plan, and respond appropriately and proportionately on blood supplies through reduced blood donation. "Maintaining a safe and adequate blood supply during the pandemic outbreak of coronavirus disease (COVID-19)" was published by WHO on 20 March. This document provides interim guidance on the management of the blood supply in response to the COVID-19 pandemic. It is intended for blood services, national health authorities, and others responsible for the provision of blood and blood components and integration of the blood system within the public health system.

The document also discusses collection of convalescent plasma as a potentially useful treatment for COVID-19. several countries are developing protocols for use of convalescent plasma.
WHO will continue to update this guidance as new information becomes available. WHO stands ready to assist countries and blood services in the follow-up - please contact maryuningsihy@who.int.

The document is available at:
https://www.who.int/publications-detail/maintaining-a-safe-and-adequate-blood-supply-during-the-pandemic-outbreak-of-coronavirus-disease-(covid-19)

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

Animal models

A WHO Working Group on Animal Models meets weekly. There has been excellent data sharing by groups working on pathogenesis models. In the most recent call, updates were provided on studies in ferrets, in which SARs-CoV-2 replicates but is clinically inapparent, and in golden Syrian hamsters which show clinical signs as well as virus replication.

The infection models are now being used to study potential treatments. A study in rhesus macaques showed significant clinical benefit from early treatment of the infected animals with Remdesevir. This is a nucleoside analogue and considered a promising candidate by WHO based on the broad antiviral spectrum, the in vitro and in-vivo data available for coronaviruses and the extensive clinical safety database (in particular coming from the Ebola virus disease clinical trial in eastern Congo).
Another group reported starting a treatment trial in non-human primates of hydroxy chloroquine, with results expected next week.

So far, models to study possible immune enhancement of COVID-19 are not available. To focus on this issue, the Coalition for Epidemic Preparedness Innovation (CEPI) and Brighton Collaboration (BC) held a virtual scientific working meeting, March 12-13, 2020 to discuss considerations on the assessment of the risk of disease enhancement with COVID-19 vaccines. The expert group convened by CEPI/BC considered evidence from previous CoV animal studies of MERS and SARS CoVs and initial data with SARS-CoV-2.

The meeting report can be obtained by sending an email to bc_coordinator@taskforce.org. Once requested, you will receive a **CDA** for you to sign. A link for accessing a restricted folder in a secure SharePoint will be sent to you upon reception so you can access the full conference pack.

Reference preparations and assay standardization activities

A network of eight WHO Collaborating Centers (CCs) (https://www.who.int/biologicals/collaborating_centers/en/) are supporting the development of international reference preparations to assist regulatory evaluations and standardization of reliable diagnostics, candidate vaccines and other biologicals.

WHO reference preparations are being prepared for both molecular and serological assays for SARS-CoV-2. Preparing candidate materials usually takes up to a year, but this time frame is being compressed into 2-3 months. The preparatory work includes the development or collection of candidate materials; carrying out preliminary studies to determine if the materials are likely to be fit for purpose; making large batches of adequate stability and sufficient to satisfy global demand over several years; and designing international collaborative studies to evaluate and validate the materials.

An international collaborative study to evaluate candidate International Standards for SARS-CoV-2 RNA, under the leadership of NIBSC, UK, is planned to start in June 2020. The standard will be used for standardisation of diagnostic assays based on nucleic acid amplification techniques (NAT) for identification of SARS-CoV-2 infection by clinical and public health laboratories, assay kit manufacturers, research laboratories and vaccine manufacturers.

An international collaborative study to evaluate candidate International Standards for SARS-CoV-2 antibodies, also under the leadership of NIBSC, UK, is planned to start in June 2020. The standard will be used for the standardisation of serological assay for identification and/or potency test of anti-SARS-CoV-2 antibodies by clinical and public health laboratories, vaccine developers, therapeutic antibody manufacturers, assay kit manufacturers and research laboratories.

For further information on either study, please contact Dr Mark Page or Dr Giada Mattiuzzo (Mark.Page@nibsc.org or Giada.Mattiuzzo@nibsc.org)

Six WHO CC laboratories are working on serological neutralisation assays, using either Pseudovirus (PsV) or wild-type virus. One WHO CC, NIFDC, China, has developed a large stock of PsV and a SOP for neutralization assays based on PsV (PBNA). The virus stock and PBNA SOP has been shared with ~~with~~ > 10 developers of vaccines or therapeutics in China. NIFDC are also developing a National Standard for SARS-CoV-2 neutralizing antibodies, and a national reference panel for NAT that will be used to evaluate various NAT kits in China.

A range of assays to help analyse the antibody response to the virus and vaccine candidates are under development by network laboratories, as are assays to quantitate SARS-CoV-2 antigen in protein-based vaccines.

Supply chain

Use of e-signature for WHO Certificates

Some National and Regional Regulatory Authorities have indicated that, during the COVID-19 crisis, they will no longer be in a position to issue and send paper copies of Certificates issued in the context of WHO Certification scheme on the quality of pharmaceutical products moving in international commerce.
Instead, and in order to maintain this critical service, they will use a secure e-signature process. WHO agrees with this initiative, which does not contradict the current WHO Guideline. WHO recommends other regulators issuing Certificates consider this approach too. NRAs receiving Certificates are urged by WHO to accept the electronic signature. This would be an example of regulatory flexibility in response to the COVID-19 pandemic.

Monitoring and responding to shortages

WHO continues to have regular calls with industry associations, procurers, international regulators, logistic networks and other organisations to assist potential supply or shortage challenges. Continuing problems are logistics and transport of API are being reported logistics networks. Transportation issues have become critical. All UN groups engaged in the topic would like to escalate this issue to the highest level possible.

Increased demand for nebulizers and inhalers is reported from all regulators as well as shortages of some **anaesthetics.** Shortages of **paracetamol, chloroquine and hydroxychloroquine** have also been reported. There are concerns about the impact of export restrictions recently introduced by India. Efforts to minimize the impact of transportation restrictions are ongoing to address needs for manufacturing materials, API and intermediate ingredients are ongoing. WHO is in regular discussion with the Indian Association of Pharmaceutical Manufacturers and the India country office.

Falsified and substandard products

The COVID-19 pandemic has increased demand and pressure on related cures, treatments and diagnostics. This has created an opportunity for ill-intended persons to distribute falsified medical products that claim to prevent, detect, treat or cure COVID-19. WHO is drafting a global alert on falsified medical products related to COVID-19, and will ensure that the messaging of the alert is accurate and actionable. This alert will differ from previous alerts because it is not product-specific and is intended to be read as a "generic warning".
The key messages of the alert, based on data available on 27 March, are

i. at this stage, there are no mass-produced commercial diagnostic kits available yet.
ii. at this stage, WHO does not recommend any specific medicinal treatment for Covid19.
iii. at this stage, there are no existing vaccines to prevent Covid19: any product currently claiming to be a vaccine for Covid19 may be considered falsified.

Of particular concern are falsified medicines from unregistered websites. Vendors may claim that their products can treat or prevent COVID-19 or may appear to provide easy access to legitimate medicines that are otherwise not readily available. Such products are likely to be falsified medicines. For further information please contact rapidalert@who.int

Disease commodity package for COVID-19 and list of medicines in the WHO COVID-19 kit

A link to the disease commodity package for COVID-19 is below, and a list of medicines in the WHO COVID-19 kit is attached.

https://www.who.int/publications-detail/disease-commodity-package---novel-coronavirus-(ncov)