Regulation of *in vitro* diagnostics, therapeutics, and vaccines

WHO Update -1

Coronavirus disease 2019 (COVID-19)

20 Mar 2020

World Health Organization

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Key messages

Current circumstances, with 209,839 confirmed COVID-19 cases and 8778 deaths reported to WHO *(as of 19 March)* and all regions of the world affected, have resulted in an unprecedented accelerated development of *in vitro* diagnostics, therapeutics, and vaccines. **Regulators in all countries are strongly urged by WHO to prioritize the rapid evaluation of all COVID-19 related applications.**

Highlights and main issues

- The first in man clinical trial of a candidate vaccine for COVID-19 has been initiated in the USA.
- With sharply increased demand for diagnostic tests, supply of sufficient quantities of reliable tests is becoming problematic. 6 countries (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 will publish links to these emergency lists, together with contact details. Due to the circumstances, these tests have not yet been through WHO assessment processes, but have been through emergency validation in the countries concerned. Also, the first dossier, for a molecular assay, has been submitted to WHO PQ requesting assessment for emergency use listing (EUL) for diagnosis of COVID-19.
- Release of the WHO COVID-19 Core Protocol for an international randomized trial of additional treatments for COVID-19 in hospitalised patients who are all receiving the local standard of care
- As of 18 March, **508 trials** related to COVID-19 are listed on the International Clinical Trials Registry Platform
- WHO is aware of concerns on the use of non-steroidal anti-inflammatory drugs (i.e., ibuprofen) for the treatment of fever for people with COVID-19. WHO is gathering further evidence on this issue before making a formal recommendation, but after a rapid review of the literature, is not aware of published clinical or population-based data on this topic.

In vitro diagnostics

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WHO continues to proceed with its emergency use listing (EUL) process, which although accelerated, requires submission of an (abridged) application and supporting clinical documentation to WHO for evaluation. 4 applications are currently under evaluation, at least 60

applicants have expressed interest and 18 applications are expected to be submitted in the coming days.

In the interests of meeting the immediate demand, WHO and FIND are collaborating on an independent, external assessment of product performance. Manufacturers are strongly encouraged to participate in the FIND-WHO Initiative to evaluate SARS-CoV-2 molecular diagnostics. The evaluation is currently focused on manual molecular assays and will contribute to the EUL assessment. It is planned to start testing automated systems shortly and an RDT evaluation protocol will follow as soon as possible. More information can be found at:

- FIND - COVID-19 outbreak: diagnostic update

Therapeutics

WHO COVID-19 Core Protocol

In early 2020 there were no approved anti-viral treatments for COVID-19, and WHO expert

groups advised that four re-purposed drugs, Remdesivir, Lopinavir (given with Ritonavir, to slow hepatic degradation), Interferon (β1b), and Chloroquine (phosphate) should be evaluated in an international randomised trial.

After expert consultation WHO has released a COVID-19 Core Protocol for an international randomized trial of additional treatments for COVID-19 in hospitalised patients who are all receiving the local standard of care. The protocol is attached.

The aim of the core protocol is to compare the effects on major outcomes in hospital of the local standard of care alone versus the local standard of care plus one of four alternative anti-viral agents. The primary objective of this large international randomised trial is to provide reliable estimates on any effects of these anti-viral treatments on in-hospital mortality in moderate and in severe COVID. The secondary objectives are to assess any effects of these anti-viral treatments on hospital duration and receipt of ventilation or intensive care, and to identify any serious adverse reactions. It is not expected that any of the treatments currently being tested will have a large effect on the risk of death, but if any had just a moderate effect and was widely practicable then this could avoid large numbers of deaths. Conversely, reliable demonstration that certain agents have no material effect on major outcomes would be of value. Moderate effects can, however, be reliably demonstrated or refuted only by large-scale randomized evidence.

Concerns on the use of non-steroidal anti-inflammatory drugs (i.e., ibuprofen)

WHO is aware of concerns on the use of non-steroidal anti-inflammatory drugs (i.e., ibuprofen) for the treatment of fever for people with COVID-19. WHO is gathering further evidence on this issue before making a formal recommendation, but after a rapid review of the literature, is not aware of published clinical or population-based data on this topic.

Vaccines

The first in man clinical trial of a candidate SARS-CoV-2 vaccine for COVID-19 was initiated in the USA. The candidate vaccine is called mRNA-1273 and was developed by US National Institute of Allergy and Infectious Diseases scientists and their collaborators at the biotechnology company Moderna, Inc., based in Cambridge, Massachusetts., USA The Coalition for Epidemic Preparedness Innovations (CEPI) supported the manufacturing of the vaccine candidate for the Phase 1 clinical trial. The vaccine candidate was developed using the sequence of the virus, not by working on the virus itself. The emerging mRNA platform has been used to develop vaccine candidates against at least 5 other respiratory viruses. After approval of the trial by the US FDA,

the first participant in the Phase 1 study was dosed, a total of 63 days from sequence selection to first human dosing.

For more information about the study, visit ClinicalTrials.gov and search identifier NCT04283461

On 18 March a TC of regulators convened by the International Coalition of Medicines Regulatory Authorities (ICMRA), co-chaired jointly by EMA and FDA, discussed initial regulatory considerations related to the development of SARS-CoV-2 vaccine candidates. Participants discussed whether proceeding to first in humans (FIH) clinical trials was acceptable in the absence of animal data addressing the theoretical risk for vaccine induced disease enhancement. A report of the meeting outcomes is expected to be available within the next few days.

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

WHO is preparing interim guidance on "Maintaining a safe and adequate blood supply during the pandemic outbreak of coronavirus disease 2019 (COVID-19)" to provide guidance on the management of the blood supply in response to the pandemic, including the possible support of the blood services for the collection of convalescent plasma for treatment of COVID-19 patients. Based on the Chinese Clinical Trial Registry (http://www.chictr.org.cn/index.aspx), several trials of Convalescent Plasma are being conducted in China. The WHO Blood Regulators Network Position Paper on Use of Convalescent Plasma, Serum or Immune Globulin Concentrates as an Element in Response to an Emerging Virus (2017) provides helpful considerations for countries considering these blood components. The Position Paper is available at

https://www.who.int/bloodproducts/brn/2017_BRN_PositionPaper_ConvalescentPlasma.pdf

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

Animal models

A WHO Working Group on Animal Models has been meeting weekly since 25 February. The group, which includes researchers, regulators and funders, agreed to share information that will help to decrease the time required to generate new candidate vaccine and therapies against SARS-CoV-2 and the disease it causes (COVID-19) and to prevent unnecessary repetition of effort. It would also support the ethical objectives of refinement, reduction and replacement in modelling research. The two current major animal model requirements are

> **Goal 1.** A model of COVID-19 disease for the evaluation and potential prioritisation of candidate interventions
>
> **Goal 2.** A model to study possible immune enhancement of COVID-19 disease

Good progress is being made, with several groups around the world reporting that non-human primates, ferrets and transgenic mice can be infected with SARS-CoV-2 strains. Although clinical signs so far reported are minimal, virus replication occurs, as does an immune response to the virus. These virological markers are considered sufficient to enable animal models to be used to help evaluate candidate interventions.

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. A report of the meeting is expected to be available in the next few days.

Clinical trials

As of 18 March, **508 trials** related to COVID-19 are listed on the International Clinical Trials Registry Platform website and can be viewed directly at

http://apps.who.int/trialsearch/AdvSearch.aspx?SearchTermStat=117&ReturnUrl=~/ListBy.aspx?TypeListing=0

Supply chain

Significant numbers of shipments of API, other components and FPPs were delayed due to the abrupt limitation on flights coming in and out of European airports. A large percentage of air freight shipments (up to 75% for some countries) for health products rely on cargo space in passenger flights. Options for alternate routes and other solutions are underway and this is expected to be a short-term issue. WHO is discussing this actively with logistics networks and with IATA.

Stock-outs and shortages of supplies for IVD's are being reported by countries. This includes shortages of media and swabs. Alternative collection media and swabs are being rapidly evaluated and submitted for regulatory approval.

WHO is convening calls on a regular basis with industry associations, including the IFPMA, IGBA and Indian Pharmaceutical Association, and regulatory groups. Currently these groups are not reporting shortages of medicines, with the exception of paracetamol and chloroquine products. All of the associations have reported that their members continue to have stocks on hand for 2-3 months. Companies are encouraged to be forthcoming with information on potential shortages, especially for critical medicines, equipment and supplies. Options to manage shortages are limited and will depend on timely implementation of solutions. If new sources are required for components or FPP, advance planning will be important.

Vaccination programs are reporting challenges with implementation, which could lead to shifts in vaccines that will need to be monitored.

Annex: Meetings on COVID19 regulatory related matters

From 31 January to 19 March, WHO RPQ have participated in app40 meetings on COVID19 regulatory related matters. A rolling list of calls and interactions is attached.

COVID-19 / Coronavirus Meetings		
Date		**Comments**
31-Jan-2020	FDA	Telecon to discuss WHO response to 2019-nCoV and requests for CBER engagement
31-Jan-2020	Medtech Europe	2019-nCoV - availability of diagnostic kits and personal protective equipment
4-Feb-2020	CEPI	JCG Meeting on nCOV-2019
5-Feb-2020	WHO Working Group	WHO nCoV R&D Summit 11-12 February - Vaccine R&D Working Group - 1st preparatory call
5-Feb-2020	WHO Working Group	WHO nCoV R&D Summit 11-12 February - Therapeutics R&D Working Group - 1st preparatory call
5-Feb-2020	IFPMA	Global supply do API/Medicines
6-Feb-2020	CEPI	Coordination
7-Feb-2020	WHO Working Group	WHO nCoV R&D Summit 11-12 February - Vaccine R&D Working Group - 2nd preparatory call
7-Feb-2020	WHO Working Group	WHO nCoV R&D Summit 11-12 February - Therapeutics R&D Working Group - 2nd preparatory call
11-Feb-2020		Expert Meeting - Novel Coronavirus
12-Feb-2020		Expert Meeting - Novel Coronavirus
14-Feb-2020	Informal contact with company	Information on shortages due to Chna crisis
17-Feb-2020	Global fund/China contact	Exchange on situation with Chinese production/supply chain issues
19-Feb-2020	FDA	Telecon to share updates on status of COVID-19 activities
19-Feb-2020	EMA	Impact of Coronavirus on supply chains
21-Feb-2020	CEPI	coordination
24-Feb-2020	Internal coordination	Diagnostics for COVID-19
24-Feb-2020	Global fund/China contact	Exchange on situation with Chinese production/supply chain issues
27-Feb-2020	WHO pharmaceutical regional advisors	DISCUSSION WITH ADG ON HOW TO ADDRESS CORONAVIRUS ISSUES TOGETHER
27-Feb-2020	WHO, IGBA, IFPMA, JAPM, Medicines for Europe	Update on supply chain issues
27-Feb-2020	MHRA/NIBSC	expert support for COVID-19
28-Feb-2020	MMV	Supply chain Security on Malaria health products
28-Feb-2020	CEPI	coordination
2-Mar-2020	WHO/ SAG	WHO R&D Blueprint Scientific Advisory Group
3-Mar-2020	WHO/GCM	WHO R&D Blueprint Global Coordination mechanism
3-Mar-2020	CEPI	Coordination
4-Mar-2020	WHO, IGBA,IPA-India, Accessible Meds	TC with Indian manufacturers - IGBA

4-Mar-2020	WHO, EMA, HHS, GMX, CEPI, Wellcome etc	COVID 19 Therapeutics Prioritization Consultation: The potential role of Interferon
4-Mar-2020	WHO, Global Fund, ICRC, Unaids, GAVI, MSF, StopTB, UNICEF, UNPA, Clinton Health Access Initiative, etc	Potential disruption on the pharmaceutical supply chain (international procurers)
5-Mar-2020	WHO, EMA, FDA, HHS, Health Canada, etc	Global regulatory teleconference discuss COVID-19 impacts on drug supply
6-Mar-2020	WHO, CEPI, CDE, NMPA, FDA, EMA	CEPI/WHO/National Medical Products Administration (NMPA) Center for Drug Evaluation (CDE) Teleconference on Registration of COVID-19 Vaccines
11-Mar-2020	EMA	COVID-19 mitigation and general touch base
12-Mar-2020	WHO, IGBA, IPA-India, Accessible Meds	TC with Indian manufacturers- IGBA
12-Mar-2020	FDA	Telecon to share updates on status of COVID-19 activities
12-Mar-2020	WHO, Canada, EMA, FDA, MHRA, etc	Global regulatory teleconference discuss COVID-19 impacts on drug supply
12-Mar-2020	CEPI organised	CEPI-BC meeting on preventing disease enhancement with COVID-19 vaccines
13-Mar-2020	CEPI organised	CEPI-BC meeting on preventing disease enhancement with COVID-19 vaccines
13-Mar-2020	Global fund/China contact	TC update on China supply chain
13-Mar-2020	WHO Therapeutics Expert Group	Consultation on the potential role of Chloroquine in COVID 19 outbreak response
17-Mar-2020	WHO, Global Fund, ICRC, Unaids, GAVI, MSF, StopTB, UNICEF, UNPA, Clinton Health Access Initiative, etc	Potential disruption on the pharmaceutical supply chain (international procurers)
19-Mar-2020	FDA	Update