21st WHO Regulatory Update on COVID-19

30 October 2020

World Health Organization

Key Messages

There is an urgency for regulatory engagement in country to help countries access World Bank funding to purchase COVID-19 vaccines. This is because WB resources for vaccine purchase will require in-country authorization, leveraging either WHO prequalification and approval by 1 Stringent Regulatory Authority (SRA) or approval by 3 SRAs in three regions.

Highlights and main issues

- A WHO Working Position on bar codes, QR codes and vaccine vial monitors has been released and is attached as Annex 1.
- Regulatory alignment and collaboration through good reliance practices is the key component that will help to facilitate equitable access to safe and effective medicines and vaccines that meet international quality and manufacturing standards. New WHO guidance on good reliance practices has been adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP).
- The vaccine pillar of the ACT accelerator, COVAX, has established a Regulatory Advisory Group (RAG) which is co-led by WHO and CEPI. The RAG meets on a monthly basis and, so far, has discussed risk-based validation approaches; GMP inspections; national regulatory authority (NRA) batch release testing; post approval changes; label requirements; expiry date; and risk management plans to monitor vaccine safety. Feedback from the RAG is provided in the format of Q&As, which are posted by WHO.
- Concerns have been expressed over the potential crossover of patients from the placebo arm of vaccine trials after the issuance of an emergency use approval. Plans for how to address the issue of potential crossover are required.
- A Brighton Collaboration Case Definition of the term "Vaccine Associated Enhanced Disease" to be utilized in the evaluation of adverse events following immunization has been published.
- The WHO COVID-19 Vaccine Prioritization Group has developed recommendations on human immune response data considered critical to evaluate phase 1 and 2 clinical trials. All manufacturers of vaccines that request consideration for inclusion in the WHO Solidarity Trial will be requested to obtain these human immune response data.
- Oxygen is one of the most essential medicines for saving patients with COVID-19, and many other conditions. Many countries simply do not have enough oxygen available. WHO has highlighted efforts to scale-up sustainable oxygen supply.

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Update on the ACT-Accelerator

Urgency for in-country regulatory engagement to help countries access World Bank funding to purchase COVID vaccines

To help countries access COVID-19 tools being developed through the ACT Accelerator, World Bank (WB) Group financing of $12Bn is available to support COVID vaccines. This support can include country participation in the COVAX facility, or direct purchases by countries from vaccine manufacturers, or purchase of excess stocks from other countries. It is likely that countries will use a combination of different options to meet their vaccine purchase needs. There is an urgency for regulatory engagement in country because WB resources for vaccine purchase will require in-country authorization, leveraging either WHO prequalification and approval by 1 Stringent Regulatory Authority (SRA) or approval by 3 SRAs in three regions.

The ACT Accelerator has 2 over-riding objectives. These are to accelerate the development of new diagnostics, treatments & vaccines and to achieve equitable global access to all COVID-19 tools. Seven months into the ACT-Accelerator there is a very promising landscape of existing & new COVID-19 tools: new Rapid Tests approved, with volume & price guarantees for LICs/LMICs (120m tests @ $3-5/unit over 6 months); 1st life-saving therapy in rollout (Dexamethasone) with 3 M doses for LICs; monoclonal antibodies in evaluation for LICs/LMICs; a dynamic vaccine portfolio; COVAX Facility 'in business' with 184+ countries & economies (>90% of world population); and the WHO Equitable Allocation Framework established. The COVAX allocation mechanism is in finalization.

Bar codes, QR codes and Vaccine Vial Monitors in the context of COVID-19 vaccines

As vaccines, therapeutics and other health products for the prevention and treatment of COVID-19 become available, they will be distributed in exceptional circumstances. Questions have been raised about the best approach to leverage technologies for automated product traceability and information sharing. WHO has released a Working Position, based on consultation with a wide range of stakeholders, to address these needs. The discussion includes two-dimensional (2D) bar-codes, quick-response codes (QR codes) and serialization technology. It also includes references to Vaccine Vial Monitors (VVMs).

In summary, 2D bar codes are included on the secondary packaging of vaccines and medicines in many markets to facilitate traceability. The WHO position recommends that this use case be applied for COVID-19 vaccines. Attempting to extend traceability technology to the vial level would only be optional and to support well-planned operational research, and only if it does not compromise statutory information on the vial label.

QR codes are also discussed in the document related to management of label and leaflet information. More specifically, expiration dates and information in leaflets (such as translations) may need to be updated after products have been released to national markets. The use of a QR code to facilitate this would be unprecedented, especially in low- and middle-income countries and it is under discussion as an option to provide supplemental information.

In considering these technologies, costs, usability, risks and benefits are likely to change over time. As such, the WHO document will remain a “working document”. The document does not define statutory label requirements for COVID-19 vaccines. A WHO Working position on labelling requirements will be released separately.

See Annex 1 for the WHO Working Position on bar codes, QR codes and vaccine vial monitors.

Alignment of approaches by regulators

COVID-19 Real-World Evidence and Observational studies

The 4th ICMRA meeting on COVID-19 Real-World Evidence observational studies discussed vaccine surveillance and vigilance; pregnancy observational research; and building international cohorts to increase study power and data quality in order to meet regulatory requirements. Additionally, members shared experiences of collaboration with academic institutions, patient organisations and other national authorities. In one country, eleven studies have been initiated so far based on existing national registries to investigate potential complications of existing treatments, such as NSAIDs and ACE/ARB, in patients with COVID-19. The report of the meeting is available at: (http://www.icmra.info/drupal/covid-19/13october2020/summary)

Good reliance practices in the regulation of medical products

The WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) met from 12-19 October 2020 inclusive. The Committee establishes international norms and standards, so that countries worldwide can regulate health products and technologies consistently. At its most recent meeting, the Committee adopted 10 general guidance texts. These included guidance on good reliance practices in the regulation of medical products. In the context of the current public health emergency, regulatory alignment and collaboration through good reliance practices is the key component that will help to facilitate equitable access to safe and effective medicines and vaccines that meet international quality and manufacturing standards.

The Committee also adopted guidance on good regulatory practices for regulation of medical products, a definition of a WHO Listed Authority (WLA) to replace the concept of SRAs, a guideline on data integrity, and an update to the WHO Certification Scheme on the quality of pharmaceutical products moving in

international commerce.

Further information is available at: https://www.who.int/groups/expert-committee-on-specifications-for-pharmaceutical-preparations

Communication tools

Expanded access to trusted information about COVID-19 on Wikipedia

Since the beginning of the pandemic, WHO has taken steps to prevent an "infodemic"— defined by the organization as "an overabundance of information and the rapid spread of misleading or fabricated news, images, and videos." WHO and the Wikimedia Foundation, the nonprofit organization that administers Wikipedia, have established a collaboration to expand the public's access to the latest and most reliable information about COVID-19. The collaboration will make trusted, public health information available at a time when countries face continuing resurgences of COVID-19 and social stability increasingly depends on the public's shared understanding of the facts. By making verified information about the pandemic available to more people on one of the world's most-visited knowledge resources, the organizations aim to help curb the infodemic and ensure everyone can access critical public health information. Information about the initiative is available at: https://www.who.int/news/item/22-10-2020-the-world-health-organization-and-wikimedia-foundation-expand-access-to-trusted-information-about-covid-19-on-wikipedia

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 and listing

Applicants are asked to submit their applications for assessment based on WHO instructions and requirements for NAT and Ag detection RDTs and IVDs detecting antibodies to SARS-CoV-2 virus. So far, 55 expressions of interest for NAT assays, 31 for antibody detection assays and 7 for antigen detection RDTs have been received. The status of each application is presented here. 22 products have been listed as eligible for WHO procurement based on their compliance with WHO EUL requirements. IVDs meeting WHO EUL requirements are listed here.

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 (26 October) was published here.

Note: **WHO does not endorse any of the lists provided by NRAs. The information is provided exclusively to assist regulators and other stakeholders with identifying the links to the various lists.**

Therapeutics

Monoclonal antibody trial in hospitalized COVID-19 patients halted

A single agent monoclonal antibody study has been halted due to futility. The antibody treatment, bamlanivimab, appears to be ineffective in treating severe cases of COVID-19. A clinical trial testing the drug in patients hospitalized with COVID-19 has been halted, but studies examining its use in early and mild-to-moderate coronavirus infections will continue.

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

Convalescent Plasma

Cochrane rapid review of convalescent plasma

Cochrane rapid reviews are simplified systematic reviews that can be done in a few weeks to produce timely evidence for decision-making. The latest of these, published on 12 October, brings together the evidence on convalescent plasma as a possible treatment for people with COVID-19. The review includes 19 studies with 38,160 people; over 36,000 of them received convalescent plasma. Two of the studies are randomized controlled trials (RCTs). These RCTs involved just 189 people in total, of whom 95 received convalescent plasma and were compared with people receiving “standard care at time of treatment without convalescent plasma”. The trials were stopped early, one because there were no more eligible people due to containment of the epidemic in Wuhan and the other because most of the people in the trial were found to have SARS-CoV-2 antibodies. Two more RCTs, completed in August, are awaiting assessment by the review authors.

The key points from the review are that the effectiveness and safety of convalescent plasma for people with COVID-19 are uncertain. The review identified 138 ongoing studies, including 73 randomized trials and, as such the results are likely to change as further data become available. The review is available at: https://www.evidentlycochrane.net/convalescent-plasma/

Adverse drug reactions

There are now 8643 reports of adverse drug reactions (ADRs) related to COVID-19 treatments in

VigiBase, the WHO global database of individual case safety reports. In this update, medicines or medicine groups of interest that have been reviewed in detail include: remdesivir, glucocorticoids,the heparin class medicines, Interleukin (IL)-6 blocking drugs (e.g. tocilizumab, sarilumab) and favipiravir.

ADR-patterns are mainly consistent with those described in earlier reports and mostly within the labelling for the respective drugs. For favipiravir, the pattern is mostly consistent with what has been described in the Japanese Pharmaceuticals and Medical Devices Agency's labelling. For remdesivir, several relevant clusters of reports of unlabelled suspected ADRs were noted.

The report is available at: https://www.who.int/medicines/regulation/medicines-safety/COVID19-PV-update13.pdf?ua=1

Vaccines

COVAX Regulatory Advisory Group

The vaccine pillar of the ACT accelerator, COVAX, [https://www.who.int/initiatives/act-accelerator] has established a Regulatory Advisory Group (RAG) which is co-led by WHO and CEPI. The RAG has members from Regulatory Agencies covering all WHO regions, including Argentina, Australia, Brazil, Canada, Europe (EMA & EDQM), Ghana, Japan, Singapore and USA.

COVAX supports vaccine developers on general matters related to vaccine development. Working groups, so called SWAT teams, have been established for manufacturing, clinical development/operations and enabling sciences to support vaccine developers in solving product agnostic challenges in COVID-19 vaccine development. The SWAT teams have members from various stakeholders such as BMGF, WHO, GAVI and industry organizations (IFPMA and DCVMN).

The RAG was set up to give feedback on regulatory science questions of an agnostic nature raised by the COVAX SWAT teams in order to promote regulatory preparedness among COVID-19 vaccine developers. The RAG meets on a monthly basis and, so far, has discussed risk-based validation approaches; GMP inspections; NRA batch release testing; post approval changes; label requirements; expiry date; and risk management plans to monitor vaccine safety.

Feedback from the RAG is communicated back to the COVAX SWAT teams in the format of Q&As. These are also posted by WHO for the benefit of all COVID-19 vaccine developers and for the wider community of regulatory authorities. The Q&As are available at: https://www.who.int/publications/m/item/frequently-asked-questions-on-regulation-of-covid-19-vaccines

US FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting

The Vaccines and Related Biological Products Advisory Committee met on October 22, 2020. The Committee discussed studies, in addition to those recommended in the US FDA June 2020 guidance for industry, that should be conducted, pre- and/or post-licensure, to evaluate the safety and efficacy of COVID-19 vaccine candidates. The inclusion of special populations (e.g., pediatric populations and pregnant women), and to the need to further evaluate the immunogenicity and duration of effectiveness of these vaccines were discussed. The Committee was also asked to discuss the need for post-marketing safety studies following approval of a COVID-19 vaccine. Furthermore, the Committee was asked to discuss what would be necessary for active safety follow up in order to permit an ongoing assessment of the benefits and risks of a COVID-19 vaccine following issuance of an Emergency Use Authorization (EUA).

The Committee discussion encompassed concerns about the risk that vaccine candidates may be biased toward prevention of mild disease and not prevention of infection, or of severe disease. There

was also concern that a vaccine that causes a 50% reduction in mild disease in absence of knowledge of whether sterilizing immunity develops may have an insufficient impact on disease spread. Concerns were raised over the potential crossover of patients from the placebo arm of ongoing trials after the issuance of an EUA, with a recommendation to continue collection of blinded data as long as possible. If blinding cannot be continued, then observational data should be considered. It was suggested that sponsors should have a plan for how to address the issue of potential crossover. The need for robust post-deployment safety surveillance was emphasized. The minutes of the meeting are expected to be available in approximately two weeks.

Brighton Collaboration case definition of the term "Vaccine-associated Enhanced Disease" (VAED)

Vaccine-associated enhanced diseases (VAED) are modified presentations of clinical infections affecting individuals exposed to a wild-type pathogen after having received a prior vaccination for the same pathogen. Vaccine-associated enhanced respiratory (VAERD) disease refers to disease with predominant involvement of the lower respiratory tract. Classic examples of VAED are atypical measles and enhanced respiratory syncytial virus (RSV) occurring after administration of inactivated vaccine for these pathogens. In this situation, severe disease has been documented resulting from infection in individuals primed with non-protective immune responses against the respective wild-type viruses.

A Brighton Collaboration Case Definition of the term "Vaccine Associated Enhanced Disease" to be utilized in the evaluation of adverse events following immunization has been published. The Case Definition was developed by a group of experts convened by the Coalition for Epidemic Preparedness Innovations (CEPI) in the context of active development of vaccines for SARS CoV- 2 vaccines and other emerging pathogens. The case definition format of the Brighton Collaboration was followed to develop a consensus definition and defined levels of certainty, after an exhaustive review of the literature and expert consultation. The document underwent peer review by the Brighton Collaboration Network and by selected Expert Reviewers.

The Case Definition is available at: https://brightoncollaboration.us/vaed/

COVID-19 vaccination SAGE October 2020 highlights now published

What key aspects should be considered in the prioritization of target populations for Covid-19 vaccination under vaccine supply constraint? This question was considered by SAGE in its October 2020 meeting. The final report will be published as usual in the Weekly Epidemiology Record and is scheduled for 4 Dec. 2020. The highlights from the meeting, all the background material and slides of the meeting have been published on the SAGE webpages at: https://www.who.int/immunization/sage/meetings/2020/october/en/ .

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 (SoF) 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, **45 vaccine candidates are in human trial**. About 10 are in or entering phase III trials. There are several others currently in phase I/II, which will enter phase III in the coming 2 months. This is a very robust pipeline – the more candidates, the more opportunities for success (typically success rate of candidate vaccines is 10%). The candidate vaccines are of various types – virus vaccines using live attenuated virus, viral vector vaccines, protein-based vaccines, and nucleic acid or RNA and DNA vaccines, which are completely new platforms.

A landscape analysis of candidate SARS-CoV-2 vaccines is regularly published by WHO. The 29 October update is available at: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

Research protocols, assays and reference standards

WHO Working Group: Assays and reference preparations

Studies of T cell immune responses to COVID-19 were the focus of the 28 October meeting. Two studies described the importance of T cells in the adaptive immune response to SARS CoV-2. Both studies found that T cell responses are associated with control of acute COVID-19. Early induction of SARS-CoV-2 specific T cells accelerated viral clearance whereas delayed induction and low numbers of SARS-CoV-2 specific T cells was seen in severe COVID-19. These findings are considered to be good signs for COVID vaccine development.

WHO Working Group: Animal models

The 35th meeting of the group, on 22 October, was open to vaccine developers. The state of the art of animal models for SARS CoV-2, based on the large amount of data shared during Working Group meetings, an unprecedented global cooperation, had been recently published (see 20th Regulatory Update). Updates since the publication included a study to show that treatment with convalescent serum decreased the severity of COVID-19 infection in non-human primates and that a study in hamsters found that neutralizing antibodies were promising as post-exposure treatment for pulmonary infection.

Recommendations from the WHO COVID-19 Vaccine Prioritization Group on human immune response data considered critical to evaluate phase 1 and 2 clinical trials were also shared with the group. All manufacturers of vaccines that request consideration for inclusion in the WHO Solidarity Trial will be requested to obtain these human immune response data.

A panel of vaccine developers then discussed two questions. The first addressed studies of the immune response in animals. Key issues on which developers are seeking academic and regulatory opinion included (a) how to bridge the immune response in animals to the human immune response (b) how long should animal studies be maintained and (c) correlates of immunity. Views expressed in the discussion were that long-term immune responses were probably better studied in humans, as evidence from other viruses, such as influenza, suggests that the kinetics of the immune response can differ between animals and humans. Further, studies of the kinetics of the human immune response after wild-type SARS CoV-2 infection are now published which would be a relevant comparator to evaluate vaccine immune responses. It was also suggested that correlates of immunity may differ between vaccine platforms.

Studies of vaccine enhanced disease were then addressed. This is a theoretical concern due to observations of enhanced disease with SARS CoV-1 in some immunization/challenge animal models. Four vaccine developers shared their experiences of testing for vaccine enhanced disease with SARS CoV-2 in a variety of animal models and with a variety of experimental designs. The discussants agreed that no signals of enhanced disease have been detected. Caution was expressed about ongoing attempts to develop positive control material for such studies since cellular constituents and media components have been shown to cause enhancement of disease that could be spuriously interpreted as caused by the virus. Likewise, outcomes of ongoing experiments involving passive transfer of sub-

optimal levels of antibody prior to challenge will need to be cautiously assessed. Such experiments will test the effect of low-levels of antibody in the absence of immune memory rather than the effects of waning antibody after immunization, in which immune memory will be present.

A review of mouse models to study SARS CoV-2 was presented in the 29 October meeting. A number of transgenic mouse strains have been developed, which develop mild disease after infection with SARS CoV-2. Recently two transgenic mouse strains, K18-hACE2 and HFH4/FoxJ1-hACE2, have been shown to develop severe lung disease. The characteristics of infections in these mice, which may be useful additional animal models to study therapies and vaccines.

Supply chain

Shortages

With the second wave of COVID-19 affecting many countries, shortages of ICU medicines are anticipated. The most recent report is of a persistent shortages of influenza vaccines. The main root cause is a sharp increase in demand and orders placed by large procuring countries to avoid concurrent COVID-19 and influenza infection.

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-lumafantrine, 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

Medical Devices

WHO Medical Devices October 2020 newsletter

The latest version of the newsletter highlights efforts to scale-up sustainable oxygen supply. Oxygen is one of the most essential medicines for saving patients with COVID-19, and many other conditions. Many countries simply do not have enough oxygen available. Estimates suggest that some of the poorest countries may have just 5 to 20 percent of the oxygen that they need for patient care. Through the pandemic, the demand for oxygen has grown exponentially. To be successful the health work force

needs to be ready. Not only doctors and nurses with experience in caring for severely ill patients; but also biomedical engineers, respiratory therapists, and maintenance staff.

The Newsletter includes updates on new documents released in October and provides information on facility surveys, country surveys, on-line training, and short-term consultancies available at WHO.

The newsletter is available by sending an email to: LISTSERV@listserv.who.int with the words: SUBSCRIBE WHOMEDICALDEVICES in the body of the message.

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

Thanks and best wishes to Emer Cooke

This is the 21st WHO Regulatory Update produced under the leadership of Emer Cooke. By the time of the next Update, she will be en-route to take up her new position as Executive Director of the European Medicines Agency. We thank Emer for her vision and drive to keep the global regulatory community updated on COVID-19 related matters through this Update and wish her all the very best in her new job!