ICMRA statement for healthcare professionals: How COVID-19 vaccines will be regulated for safety and effectiveness

Statement from the International Coalition of Medicines Regulatory Authorities

Healthcare professionals and public health authorities will have a central role in discussing vaccination against COVID-19 with their patients.

Despite a large number of clinical trials and extensive global development underway, to date there are still few effective anti-viral medicines for the treatment of COVID-19 infection. This makes the role of vaccines for COVID-19 even more important.

The global impact of the COVID-19 pandemic has resulted in an unprecedented level of public interest in vaccines and their development and regulatory review. This has taken place mainly through mass and social media. The same channels have also led to a significant amount of misinformation and disinformation circulating about the pandemic. This may lead some to express concerns about getting vaccinated - or even be strongly opposed to vaccination. Another challenge in communicating the importance of COVID-19 vaccination is that so far, globally, younger adults are typically less clinically affected by COVID-19 infection and could see limited value in getting vaccinated, although they may have personal experience or come in contact with family members or friends affected by serious COVID-19 disease.

We appreciate that you, your colleagues and your patients may have a number of questions around the development, regulatory review and ongoing safety monitoring of COVID-19 vaccines.

The rapid development of COVID-19 vaccines, with many using new technologies, the comparatively short clinical trials and the proposed use of conditional, provisional or emergency use authorisation regulatory processes may leave healthcare providers and patients with questions and concerns. It is also likely that several different COVID-19 vaccines, based on different technologies, will become available over the coming year.

This statement explains the regulatory processes associated with the review of COVID-19 vaccines for safety, efficacy and quality. It also explains the arrangements put in place both nationally and globally for ongoing safety monitoring of different COVID-19 vaccines once they are on the market.

It is widely anticipated that vaccination against COVID-19 will be instrumental in ending the global pandemic and saving lives.

Purpose

This International Coalition of Medicines Regulatory Authorities (ICMRA)[*] statement aims to inform and help healthcare professionals answer questions about the role of regulators in the oversight of COVID-19 vaccines. It explains how vaccines undergo robust scientific evaluation to determine their safety, efficacy and quality and how safety will continue to be closely monitored after approval.

People who are not vaccinated remain at risk of spreading the virus. Herd immunity through vaccination occurs when the majority of population has been vaccinated and can no longer give the virus to others, hence protecting themselves as well as those who cannot be vaccinated. Achieving 'herd immunity' and reducing the effective reproduction number of infection disease as much as possible is important. If 'herd immunity' is not achieved by enough people being vaccinated this could seriously affect vulnerable people, including immunocompromised people who cannot receive vaccines, or those who respond poorly to vaccination and therefore are more readily infected. Herd immunity requires a combination of high vaccination coverage with vaccines that are both effective and provide a reasonable duration of protection. Achieving 'herd immunity' will allow a return to normal societal functioning and re-opening of economies.

Vaccines and the regulatory process

How will regulatory authorities evaluate COVID-19 vaccines?

Regulators independently and rigorously evaluate scientific and clinical evidence provided by industry sponsors of vaccines, as well as other available evidence. Each vaccine is thoroughly assessed for safety, efficacy and pharmaceutical quality to determine whether it can be authorised, using available scientific evidence from animal data, human clinical trials, and manufacturing information to assess its benefits and risks.

Public health agencies develop and deliver vaccination programs. Often working with their expert immunisation technical advisory committees, this includes prioritising populations for vaccination, issuing additional recommendations and providing information about vaccines and immunization. They also collaborate with regulators to monitor vaccine safety after they are approved for use.

Safety evidence prior to potential approval:

Safety evidence is an essential part of the regulatory submission for COVID-19 vaccines as they will be administered globally to help control the pandemic. Safety evidence is gathered during all phases of the vaccine development process.

Both common and infrequent side effects need to be examined and reported in the regulatory submission. Typically, regulators will require that participants in clinical trials have been followed for at least 1-2 months after receiving their final vaccine dose. Based on previous experience with vaccines the most serious (but very rare) adverse events appear within such timeframes. There will also be longer term (over 6 months) follow up of those who participated in the earlier phases of the clinical trials of each vaccine. Many trial participants will also be followed for at least 1 year to assess the duration of protection and longer-term safety of individual vaccines.

Efficacy:

Apart from information on the types of immune responses induced by the vaccine, data in well-designed clinical trials must be submitted to regulators to demonstrate that the vaccine does in fact

prevent COVID-19 in sufficient numbers of subjects (generally, at least 10,000 and usually about 30,000), representing a spread of age groups and subjects with co-morbidities. Given the disproportionate impact of COVID-19 on the elderly, most developers of COVID-19 vaccines have included significant numbers of elderly participants in clinical trials.

The safety and efficacy of each vaccine are also carefully evaluated independently on a product by product basis. Clinical trials should show that a candidate vaccine very significantly reduces COVID-19 in people who are vaccinated, compared to a control group of people who don't receive the vaccine, through a reduction in numbers of laboratory confirmed SARS-CoV-2 infections. It is expected that candidate vaccines should also reduce the transmission of disease between individuals.

Regulators may seek additional independent expert advice from independent scientific advisory committees to help inform their decision on whether to approve a vaccine. These committees are made up of experts in science, medicine (including infectious diseases) and public health and often include consumer representatives.

Quality:

Any COVID-19 vaccine that receives regulatory approval must be manufactured according to internationally agreed stringent regulatory standards of good manufacturing practices (GMP). Regulators will review data to confirm that the manufacturing process at each production site is well controlled and consistent. This will include data on the identity and purity of the vaccine components and its potency, as well as data on every step of manufacturing and on the controls used to ensure that each batch of vaccine is consistently of a high quality. Data on vaccine stability must also be provided before a vaccine can be approved. Batches may also undergo evaluation by individual national regulatory authorities to ensure they meet international requirements, before they can be supplied.

Monitoring safety and effectiveness after vaccine approval:

After a vaccine is authorised, sponsors will be required to conduct robust safety and effectiveness monitoring (pharmacovigilance) and risk minimisation activities. They will need to continuously monitor vaccine safety to ensure that the benefits of the vaccine continue to outweigh the risks. To this end, regulators require vaccine sponsors to have risk management plans describing how they will undertake to monitor and minimise risks associated with their vaccines. Vaccine companies will also be required to continue safety surveillance from the ongoing clinical trials of their products, typically using a number of approaches:

- Reviewing and analysing adverse events reported by healthcare professionals and consumers and requiring industry vaccine sponsors to report to regulators on adverse events received both within the regulator's home country and globally;
- Many regulators will implement enhanced passive surveillance systems, and will have access to near real-time data on vaccine usage in different settings. Several will also implement traceability systems for different vaccine brands and batches;
- Working with other international regulators and researchers to share information about emerging safety issues in order to take quick action to mitigate risks; and
- Reviewing medical literature and other sources of new safety information.

It is very important that healthcare professionals not only diligently report adverse events that they see in their patients, but to also encourage people who are vaccinated to immediately report them to their healthcare professionals.

Regulators will develop lists of "Adverse Events of Special Interest" following vaccination. Some have been rarely associated with immunization and others are often reported but have not been found to have a causal association. Having background rates of these events will help ensure that any increases detected can be quickly verified. If a significantly increased frequency of certain serious adverse events is detected in vaccinated groups, then this will lead rapidly to regulatory actions.

The widespread use of COVID-19 vaccines, including in the elderly, will unfortunately mean that there will be many purely coincidental deaths and serious illnesses, unrelated to vaccinations. The job of each regulator is to establish causality – in other words, whether the vaccination is likely to have led to the serious outcome. There will also be a special focus on monitoring safety in pregnant women, persons with severe pre-existing illness, the elderly and children and interaction with other vaccines.

Regulators, in collaboration with public health authorities, are able to take decisive action if and when a safety issue is identified. These actions might include issuing safety communications for patients, healthcare professionals and the community; updating the product information or consumer information for the vaccine; preventing the release of a particular batch of vaccine; and, taking other regulatory actions as necessary.

Globally, the public can have confidence in the rigour of the process used to scientifically evaluate the safety, efficacy and quality of vaccines before they are approved for use in the wider population.

Questions and Answers on COVID-19 vaccines

Q: How have the vaccines been developed so quickly? Does this mean that their safety and efficacy has been compromised?

A: The speed of development of COVID-19 vaccines has been unprecedented for several reasons

- **The massive financial investment** by governments - in the tens of billions of dollars or more, in vaccine development and the re-direction of much of the global research and commercial vaccine developing and manufacturing infrastructure. This also enabled companies to take the commercial risk of manufacturing some vaccine stocks ahead of regulatory approvals as governments underwrote the risks of costs of failure.
- **New technologies adapted from the development of other vaccines** – mRNA vaccines were developed very rapidly after the sequence of the COVID-19 virus was determined, and production was scaled up very quickly. The adenovirus technology used in another type of vaccine was first tested with SARS and MERS over the last 20 years, and so was able to be adapted quickly to COVID-19, which has several similarities to these viruses.
- **Clinical trial successes** - because of the high concerns about COVID-19, it has been possible to rapidly recruit large numbers of volunteers into clinical trials and, with unfortunately high rates of infection in several countries, complete trials using 10,000-50,000 subjects in a short period of time. Under normal circumstances, it may take many months or even a few years to determine whether a vaccine is effective.
- **Very close collaboration** - between regulators, industry and clinical researchers enabled clear indications of regulatory requirements and early access to results.
- **Intensive and insightful research**. Researchers predicted that the "spike protein" on the virus would be a good target for vaccine development, and almost all vaccines have used this part of the viral sequence. So far, the spike protein has produced a strong immune response in those vaccinated, and for those vaccines that have reported clinical results, high efficacy of protection from COVID-19 disease.

Q: Will mRNA vaccines affect the DNA of vaccinated patients?

- A: No. The mRNA in the vaccine cannot incorporate itself into the genes of vaccinated patients and generally breaks down in the weeks after vaccination. mRNA vaccines contain genetic instructions for our cells, which only read them and provide copies of the SARS-CoV2 spike protein that enables the cellular and antibody immune systems to cause a response in vaccinated patients.

Q: How long will COVID-19 vaccination provide protection for immunised people?

- A: The experience with other vaccines shows variable durations of protection. For example, the seasonal influenza requires annual vaccinations, because the virus mutates. Other vaccines, such as those for rubella or measles provide multi-year or even life-long protection from disease. While there appears to be some mutation of the SARS-2-coronavirus, results to date indicate that mutations are limited, not necessarily affecting the target of the vaccines. The scientific community and regulators will monitor whether the coronavirus SARS-CoV-2 changes over time and, if so, whether vaccines can continue protecting people from infection with new variants.

- However, we do not yet know how long protection from any of these vaccines lasts. We will get better insights in 2021 and 2022.

Q: Why are there so many vaccine candidates?

- A: As the global seriousness of the pandemic became rapidly apparent, development of effective vaccines for COVID-19 became the top priority of many pharmaceutical companies and medical research institutes. There was also unprecedented government and private sector investment on vaccine development. There is now a wide range of technologies for developing new vaccines - and many of the organisations developing COVID-19 vaccines have particular experience in one or more of these technologies.
- The World Health Organisation (WHO) and governments have encouraged the development of vaccines based on a wide range of technologies and this mitigated the risk that some vaccines could fail regulatory approval for reasons of efficacy, safety or manufacturing challenges.
- Developing a range of vaccine technologies has been an effective way of risk mitigation.

Q: What if many people start getting a reaction from a particular COVID-19 vaccine?

- A: Short-term reactions, such as soreness at the injection site, fatigue or headache are common following vaccination. These reactions usually pass in a day or two.
- If serious adverse events emerge for a particular vaccine then regulators will take action, working collaboratively and on a global basis and liaise with public health authorities. The type of actions that can be taken depend on the nature of the adverse event, and could range from warnings to closely monitoring adverse events in certain groups of patients, to contraindicating the use of the vaccine in particular patients (e.g. those with certain co-morbidities) through to temporary suspension of the use of the vaccine until more is known.

Q: What are "faster access pathways"? How are regulators speeding up the time it takes to authorise a COVID-19 vaccine?

- A: Many regulators globally have implemented faster access pathways for COVID-19 vaccines.
- Some countries have Emergency Use Authorisation pathways which assess the limited available data at the time of authorisation. Exercising these provisions is a matter for those countries, taking into account the risks versus benefits in the context of the prevailing domestic pandemic situation.
- Other countries have implemented accelerated/priority, conditional or provisional approval schemes. Under normal circumstances, regulatory assessment begins once all information to support registration is available. For COVID-19 vaccines, many regulators have agreed to accept data on a rolling basis to enable early evaluation of data as it becomes available. Regulators will only be in a position to make a provisional registration decision for a vaccine once all required data has been provided and assessed and the safety, quality and effectiveness of the vaccine has been satisfactorily established for its intended use. If a decision is made to grant provisional or conditional registration, it will be based on the requirement for the sponsor to submit more comprehensive, longer term clinical data, stability data and other information with agreed timelines.
- The implementation of various accelerated regulatory pathways in combination with international collaboration between regulators and proactive work with sponsors is expected

to significantly expedite the evaluation of COVID-19 vaccines without compromising on strict standards of safety, quality and efficacy.

Q: Did our country approve this COVID-19 vaccine, or are we relying on another country's approval?

- While there is unprecedented collaboration between regulators in different countries on COVID-19 vaccines, including discussion and sharing of product assessments, most countries are carrying out independent regulatory evaluations on the submitted data for each vaccine. However, regulators are communicating closely on safety, efficacy and quality data and discussing technical issues as they may arise. This approach provides the best of both worlds, independent decision making coupled with the expertise of scientists working globally together.

About ICMRA

ICMRA brings together the heads of 30 medicines regulatory authorities[1] from every region in the world, with the WHO as an observer. Medicines regulators recognise their important role in facilitating the provision of access to safe and effective high-quality medicinal products that are essential to human health and well-being. This includes ensuring that the benefits of vaccines outweigh their risks.

[1] ICMRA is an international executive-level coalition of key regulators from every region in the world. It provides a global strategic focus for medicines regulators and gives strategic leadership on shared regulatory issues and challenges. Priorities include coordinated response to crisis situations. Members of the ICMRA include: Therapeutic Goods Administration (TGA), Australia; National Health Surveillance (ANVISA), Brazil; Health Products and Food Branch, Health Canada (HPFB-HC), Canada; China National Medical Products Administration (NMPA), China; European Medicines Agency (EMA) and European Commission - Directorate General for Health and Food Safety (DG - SANTE), European Union; French National Agency for Medicines and Health Products Safety (ANSM), France; Paul-Ehrlich-Institute (PEI), Germany; Health Product Regulatory Authority (HPRA), Ireland; Italian Medicines Agency (AIFA), Italy; Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA), Japan; Ministry of Food and Drug Safety (MFDS), Korea; Federal Commission for the Protection against Sanitary Risks (COFEPRIS), Mexico; Medicines Evaluation Board (MEB), Netherlands; Medsafe, Clinical Leadership, Protection & Regulation, Ministry of Health, New Zealand; National Agency for Food Drug Administration and Control (NAFDAC), Nigeria; Health Sciences Authority (HSA), Saudi Arabia Food and Drug Administration (SFDA); Singapore; Medicines Control Council (MCC), South Africa; Medical Products Agency, Sweden; Swissmedic, Switzerland; Medicines and Healthcare Products Regulatory Agency (MHRA), United Kingdom; Food and Drug Administration (FDA), United States and the World Health Organization as an observer. Associate members include Austrian Medicines and Medical Devices Agency (AGES), Danish Medicines Agency, Israel Office of MedicalTechnology, Health Information and Research (MTHIR), Poland Office of Registration of Medicinal Products and Biocidal Products (URPLWMiPB), Russia Roszdravnadzor and Spain Agencia Española de Medicametos y Productos Sanitarios (AEMPS).