CoRE Regulatory Perspective

Regulatory Agility and Global Coordination to Meet the Challenge of Covid-19 Variants: Preparing for the Next-Generation Vaccines

15 March 2021

Please note that this is a rapidly evolving topic and the information presented in this article is accurate as of 15 March 2021.

Regulatory agility[1] and global cooperation have enabled timely access to several vaccines for COVID-19 through emergency use pathways[2] and conditional authorisations while maintaining rigorous standards for assessing safety and efficacy. As countries begin their vaccination initiatives, new challenges have emerged such as ensuring adequate vaccine supply, equitable distribution and combatting evolving virus variants. Currently authorised vaccines still provide an acceptable level of protection against severe disease from even the new variants that are causing concern. Scientists, industry and national regulatory agencies (NRAs) must remain vigilant and agile to stay ahead of the virus and mount a timely, coordinated response should currently authorised vaccines need to be updated.

What are SARS-CoV-2 variants and why are they important to monitor?

It is expected that mutations will occur in RNA viruses over time. To give clarity on what makes a variant more worrying, the World Health Organisation (WHO) has provided working definitions[3] to distinguish between variants of interest (VOI) and variants of concern (VOC). The latter are those that may impact transmission, disease severity or accuracy of diagnostics. Several SARS-CoV-2 variants of concern have been identified in different parts of the world such as in the UK (B.1.1.7), in South Africa (B.1.351), and Brazil (P.1). All these variants carry multiple mutations in the spike protein of SARS-CoV-2, which is the target for most of our current vaccines.

Will currently authorised vaccines work against the known variants of concern in circulation?

The pivotal trials for most of the authorised vaccines were conducted before the VOCs were in wide circulation. Preliminary results from *in vitro* studies show that sera from vaccinated individuals does not have significantly lower neutralising antibody activity against the B.1.1.7 variant but there is more pronounced reduction in neutralisation against the B.1.351 variant and the P.1 variant[4,5,6]. It is important to note that *in vitro* neutralisation antibody studies do not give a full picture of the immune response, which is complex and multi-layered. There is encouraging clinical data from the trial of the recently authorised Janssen Ad26.COV2.S vaccine[7] which showed efficacy in preventing severe disease was still high despite circulating VOCs.

The potential of new variants emerging in the future that may significantly reduce vaccine efficacy is concerning and demands urgent actions to control the spread of the virus by scaling up current vaccination programmes to reduce opportunities for new variants to develop. The world should also prepare for the development of the next generation of updated vaccines to address existing and emerging variants of

concern. Updates may also be beneficial to develop vaccines that are more heat-stable and are even more effective at preventing infection and not just severe disease.

How are regulatory agencies approaching the variants of concern?

NRAs and vaccine manufacturers have considerable experience with modifying and updating the influenza vaccines annually based on the circulating strains. The global effort[8] is coordinated by the WHO and involves many organisations and research centres. NRAs are leveraging on past approaches to influenza vaccine, which has an abridged process for seasonal updates, to formulate the guidance for data on vaccines against SARS-CoV-2 variants. However, COVID-19 is *not* influenza and is still a relatively new disease. Hence, regulators are being more cautious in requiring more data than is usually submitted for updating of seasonal influenza vaccines.

Regulatory cooperation and convergence are key to ensuring a consistent and timely response to emerging variants in an ongoing pandemic. To promote convergence[1], the International Coalition of Medicines Regulatory Authorities (ICMRA) held a COVID-19 variants workshop[9] in February 2021 to discuss minimal data requirements to facilitate expedited approval of updated versions of currently authorised vaccines to address emerging variants. The United States Food and Drug Administration (US FDA)[10], European Medicines Agency (EMA)[11] and the ACCESS Consortium[12](a coalition of the regulatory agencies of Australia, Canada, Singapore, Switzerland and the United Kingdom) have since published their preliminary guidances. It is heartening that their approaches are similar and in line with the principles outlined at the ICMRA meeting. NRAs should continue to converge their guidances, where feasible, on data requirements for next-generation COVID-19 vaccines.

Quality Data Requirements

The specific requirements for quality data would depend on the vaccine platform, e.g. mRNA vaccine, viral vector, purified protein produced by recombinant DNA technology or inactivated viral vaccine. Regulators expect that the manufacturing process and controls for the parent vaccine and variant vaccine will be similar and scientific justification would be required for any changes in process.

Non-clinical Data Requirements

[1] Regulatory convergence is where regulations in different countries become more aligned over time with adoption of internationally recognised technical guidance documents, standards, and scientific principles, while taking into account distinctive national legislative, demographic and risk-tolerance factors

For EMA, there is no requirement to conduct any further in-vitro or in-vivo nonclinical testing to support the development of variant vaccines. The FDA and the ACCESS Consortium have not mandated any non-clinical studies but may request data depending on the platform and data available from parent strain vaccine. FDA and the ACCESS consortium have also encouraged, but not mandated, studies in relevant animal models to add to the totality of evidence. Manufacturers should work closely with regulatory authorities to justify their choices of non-clinical evidence to include or exclude in support of updated vaccines.

Clinical Data Requirements

The current guidance from agencies does not require the repeat of large, lengthy clinical efficacy trials for modified vaccines. An inference of efficacy should be supported by data from smaller clinical immunogenicity and safety studies. The FDA and EMA have outlined the designs for non-inferiority studies comparing the parent vaccine and the modified one recommending at least one trial in unvaccinated populations if feasible. Booster trials are recommended in populations that have already been vaccinated. The ACCESS Consortium guidance welcomes discussions on alternative designs if non-inferiority comparison study of parent vaccine and updated vaccines is not appropriate.

The UK Medicines and Healthcare products Regulatory Agency (MHRA) has specified some considerations for updating vaccines in the United Kingdom, beyond those outlined in the ACCESS Consortium statement. For example, the MHRA is open to discussing human challenge studies where a model is available for the new variant. Proponents of the use of human challenge studies in the evaluation of COVID-19 vaccines argue that they offer a more direct and efficient way to study and compare vaccines[13]. There is continued debate on the ethical issues surrounding human challenge studies such as a potentially unfair risk to participants even if young and healthy people are selected.

Future Outlook for Regulation of Modified Vaccines

Vaccine manufacturers Moderna[14] and Pfizer[15] are already conducting trials to explore strategies to extend protection against the B.1.351 variant. The US FDA has encouraged manufacturers to perform such exploratory studies in its guidance, but it is not guaranteed that strains being explored by companies would ultimately be selected for development of a modified vaccine. It is still unclear what data would indicate the need for a modified vaccine and what agency or entity would evaluate, decide and recommend whether a modified vaccine is needed. The WHO is well placed to facilitate a global regulatory approach, as they do for seasonal influenza vaccines, and is engaging with global NRAs to discuss this issue. There is also discussion on the merits of centralised international regulatory control to harmonise

the genetic sequence of the updated antigen, but this approach may slow down development of new vaccines, as highlighted in the ACCESS Consortium statement

Another important challenge is that there are still no validated immune correlates of protection (CoP) for COVID-19 [16]. Some agencies are recommending developers use neutralising antibody assays for now, but the minimum level of antibody titres corresponding to clinical protection in the human body has not been established yet. A validated CoP is important because it can potentially be used as a surrogate endpoint for assessing vaccine efficacy without conducting time- and resource-intensive clinical studies. A CoP that is acceptable to regulators would reduce the time it would take to develop modified vaccines and expedite regulatory approval.

The current guidance frameworks are only preliminary and will likely be adjusted as new data emerges over time. The interim guidance does offer some insights into the thinking of NRAs for the future. The EMA reflection paper has considered various potential future scenarios for example, if an immune correlate of protection were in place. The ACCESS Consortium is already contemplating how guidance developed for COVID-19 vaccines could be used for future pandemics by creating “core dossiers” for future vaccines against other coronaviruses.

Priorities for Global Coordination to Address Variants of Concern

NRAs are working to converge their regulatory approaches through global platforms such as ICMRA and by engaging with the WHO. Regulatory agencies do not exist in a vacuum and a global, holistic approach is needed to monitor and respond to VOCs. The global health community should coordinate to support capacity-building for national and regional public health laboratories for genomic surveillance[17] especially in lower and middle income countries. There is also a compelling need for global standards and data-sharing platforms[18] for observational data on vaccines to be able to track their real-world effectiveness against variants most efficiently and widely. It is important to effectively communicate the current scientific uncertainties to the public while avoiding stoking unnecessary fear about variants. Countries should continue to scale up immunisation with current vaccines and adhere to existing public health measures to slow emergence and impact of variants.

Table 1. Summary of global NRA interim guidance on regulatory requirements for updated COVID-19 vaccines for new strains of SARS-CoV-2 as of March 9, 2020

	US FDA (Feb 2021)	EMA (Feb 2021)	ACCESS Consortium* (March 2021)
Criteria for requiring updated vaccines	All the regulatory agencies continue to discuss the guidance to be issued on data indicating the need for a modified vaccine		
Multivalent vaccines	Does not address considerations for multivalent vaccines	Guidance applicable to both monovalent and multivalent vaccines	Considerations for additional immunogenicity studies to be discussed with individual regulatory authorities
CMC	CMC data depend on the vaccine platform and assume that the manufacturing process, facilities and controls for production are similar to prototype vaccine. All the agencies require the minimum updated CMC data as relevant to the modified vaccine.		
Nonclinical	Studies on relevant animal model contribute to totality of evidence and are encouraged. Additional repeat dose toxicity studies are not required.	There is no requirement to conduct any further in-vitro or in-vivo non-clinical testing to support the development of variant vaccines.	Non-clinical immunogenicity data in a relevant animal model will be informative. Lack of toxicity studies would need justification.
Clinical	Both agencies would infer efficacy from clinical immunogenicity and safety data as a surrogate for large trials. The agencies recommend at least one comparative study of the immune response induced by the modified COVID-19 vaccine to the prototype vaccine in unvaccinated population where feasible. Criteria, design and statistical considerations for non-inferiority studies have been specified.		Design considerations for non-inferiority immunogenicity studies discussed. Other designs may be discussed with agencies where comparative non-inferiority studies are not appropriate.

* Human Challenge study considerations are mentioned in the addendum to ACCESS Consortium statement by UK MHRA to be discussed with the agency, but this is not included by other participating regulatory authorities of the ACCESS consortium.

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