Overview

The vaccine pillar, COVAX, of the 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, India, Japan, Republic of Korea, Singapore, UK and USA.

COVAX also 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. Feedback from the RAG is communicated back to the COVAX SWAT teams. It is also presented here, in the form of a Technical Brief, for the benefit of all COVID-19 vaccine developers and for the wider community of regulatory authorities.

The RAG applies the Chatham House rule, and divergent views are reported as such without attribution. However, for some subject matters, the RAG members have agreed that country specific recommendations/guidance may be reported/attributed.

Information discussed in the RAG meetings from August 2020 to February 2021 is summarized and published in the Technical Brief issued on 14th April 2021.

May 2021 issue of the Technical Brief includes the information of the 15 April 2021 RAG meeting.

This June 2021 issue includes the summary of the May 2021 RAG discussion on ‘Immunobridging within same vaccine platform: endpoints and trial population’.

For any questions, please contact COVAX-Reg@who.int.

Evaluation of vaccines addressing SARS-CoV-2 variants

Immunobridging within same vaccine platform: endpoints and trial population

Pre-read material had been distributed from the Clinical and Operations SWAT Team to the RAG to address questions about immunobridging non-inferiority clinical studies for vaccines targeting SARS-CoV-2 variants within the same platform.

The scenario discussed was variant-adapted vaccines for which vaccine efficacy based on a ‘prototype’ vaccine based on the original SARS-CoV-2 strain had been demonstrated. Proposed definitions for harmonized proportionate endpoints were included in the pre-reads.

It was suggested that these endpoints (in addition to geometric mean neutralizing antibody titers (GMTs) would be used in one single Phase 3 non-inferiority clinical study that would generate supportive data with the aim of registration/authorization in different world regions. Seropositive as well as seronegative population would be assessed based on these endpoints. It was also indicated that the scenario for vaccines with an established efficacy of 60% or less should be discussed with regulators.
Requests to the RAG:

Does the RAG agree with the proposed approach and endpoint definition for the proportionate immune response in addition to GMTs which is applicable to both, initially seronegative and seropositive populations?

Feedback:

- RAG members welcomed the proposal and agreed with the overall objective of achieving harmonized endpoints.
- It was noted that discussions are still ongoing within regulatory authorities as to how these endpoints should be defined. As more data arise and the level of knowledge increases, harmonization is more likely to occur.
- It was proposed that regulators should have further discussions in regulatory forums with NRAs/cluster teleconferences with the aim of achieving harmonization of endpoints.
- Awareness was raised about the benefit to vaccine developers of harmonized endpoints, as developers generally conduct a single clinical trial that will gather data to make informed decisions and filings in different world regions.
- Multiple elements need to be considered such as the type of assays used for these endpoints; the population, in particular previously infected individuals or seropositive at baseline; or the appropriate minimum factor for titre increase post- vs. pre-vaccination.
- It was mentioned that for other types of vaccines a minimum of 4-fold titre increase (post- vs. pre-vaccination) had been deemed adequate.
- With regards to single-dose booster vaccination strategies assessed via immunobridging, it was noted that this will become the most likely scenario as vaccination rates continue to increase and hence the available pool of naïve individuals, and in particular elderly, decreases. The existing reflection papers/guidelines on variants include this kind of scenario (and the desired primary outcome). It is anticipated that this will evolve as more data and knowledge are gathered.
- The importance of gathering data via conducting “exploratory” clinical studies (i.e. studies with a cohort of vaccinees receiving a booster of variant vaccine) was highlighted as these data will be helpful in further refining the endpoint definitions and statistical criteria and will aid global harmonisation. Characterization of the immune response elicited by the vaccine variant and of the baseline status are regarded as key components in these exploratory studies.
- The RAG agreed that the clinical assessment strategy for vaccines with 60% (or less) efficacy should be discussed with regulators.