Access Consortium: Alignment with ICMRA consensus on immunobridging for authorizing new COVID-19 vaccines

Placebo-controlled disease endpoint trial data are the gold standard for authorizing vaccines. However, for COVID-19 vaccines, it is difficult to conduct efficacy trials in some countries, as few candidates are willing and available to participate. Without established humoral and/or cellular immune parameters that correlate to clinical protection against disease, other approaches are needed to provide sufficient evidence for authorizing new COVID-19 vaccines.

The International Coalition of Medicines Regulatory Authorities (ICMRA) convened a workshop on June 24, 2021, to consider the development of COVID-19 vaccines. The ICMRA focused on immunobridging, the design and use of controlled trials (placebo or other controls) and correlates of protection.

Access Consortium members agree that well-justified and appropriately designed immunobridging studies are an acceptable approach for authorizing COVID-19 vaccines.

The Consortium provides additional considerations for cross-platform immunobridging. These include extending previous points of consideration for variant-based vaccines that was limited to currently authorized COVID-19 vaccines.

Consensus positions from the ICMRA meeting relevant to this statement include:

- study designs for pivotal trials to demonstrate the efficacy of COVID-19 vaccines must provide robust data for authorization
- immunogenicity bridging studies can be used if clinical endpoint efficacy studies are no longer feasible
- study designs can be based on either:
    - non-inferiority immunogenicity if the comparator vaccine has demonstrated high efficacy in clinical diseases endpoint efficacy trials and/or
    - superiority if the comparator vaccine has demonstrated modest efficacy
- based on the specifics of the product under consideration, neutralizing antibody titre may be justified as immune marker to predict vaccine effectiveness
- neutralizing antibody titres should be determined using World Health Organization (WHO)-certified reference standards
- other parameters to be justified include:
    - choice of appropriate vaccine comparators considering the platform
    - statistical criteria
    - population comparator groups (for example, matched by age, gender, prior vaccination/infection status)
- applicant support of sharing information between regulators would help build global convergence

The Access Consortium considers that the weight of evidence from studies with authorized COVID-19 vaccines is sufficient to support using neutralizing antibody titres as a primary endpoint in cross-platform immunobridging trials.

Applicants are to provide a clear rationale regarding the:

- suitability of neutralizing antibody as a primary endpoint in immunobridging studies, considering data that support the mechanism of action for the candidate vaccine
- the proposed comparator and an appropriate design (for example, comparability margin)

The Consortium also recommends that applicants follow WHO standards in neutralization assays and consult with the relevant authority early on in the study process.

Applicants are also to provide the following:

Non-clinical data

As well as common non-clinical requirements for new vaccines and adjuvants, non-clinical data should include:

- relevant animal challenge studies that support proof of concept for the candidate vaccine and demonstrate effectiveness against variants of concern (VOCs)
- characterization of comparative immunogenicity profiles, including both antibody- and cell-mediated immunity

Clinical data

Along with a comparison of neutralizing antibody titres, clinical data should include:

- characterization of comparative immunogenicity profiles, including cell-mediated immunity
- characterization of comparative in vitro neutralization against VOCs
- safety database of at least 3,000 study participants vaccinated with the dosing regimen intended for authorization (this is in line with the pre-authorization safety data requirements for preventive vaccines for infectious diseases)
- commitment for safety and immunogenicity follow-up for at least 12 months of the subjects enrolled in safety/immunobridging trials, which would also record descriptive clinical efficacy data
- commitment for post-authorization effectiveness studies supported with a study protocol considering current WHO guidance

Applicants are also advised to consult the following:

Access Consortium statement on authorisations of modified Covid-19 vaccines for variants (swissmedic.ch)