Defined Thresholds Versus Ranges for Immune Responses & Immunological Endpoints for New Vaccine Evaluations

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Outline

• Consideration of challenges with the landscape of approved, under review and, pipeline vaccines.

• A rational basis for hypothesis testing, what are “the right questions”?

• Requirement for scientifically based, rigorous yet expedited authorization paths for:
  • Booster vaccines
  • New vaccines
Considering the Vaccine Landscape

• All current authorized vaccines are based on original strain virus.

• Authorized initial vaccines with efficacy data were matched to original strain, but this shifted with evolving variants with latter efficacy trials.

• Regardless, current effectiveness data for vaccines, with high initial efficacy against original strain, still prevent serious disease and hospitalization against more challenging VOCs (beta, gamma, delta).

• Hence, even with reduced neutralization against VOCs, efficacy can be inferred though immunobridging for VOC vaccine designs, but how should this be assessed? Also, for vaccines still in early development, a VOC design may be a preferred option, but requires data to support such a choice.
Assessing New VOC Vaccines: The “Right Questions” to Ask for Immunobridging

• While disease endpoint data will always be considered, under current guidance and regulatory considerations for strain changes with authorized vaccines (i.e., immunobridging within platform) non-inferiority against original strain is required. However, is this asking the appropriate question in the current context?

• While efficacy data is against original strain, circulating VOCs are the functional target, not the original strain, the latter of which was more relevant earlier in the pandemic.

• Hence, evaluation of non-inferiority of a prototype vaccine vs a VOC vaccine, against VOCs of interest is perhaps a more relevant consideration.
Assessing New VOC Vaccines Cont’d

• Information related to the immunogenicity of a VOC design vaccine to origin strain may be of interest. However, it may be an inappropriate choice for a primary endpoint if a strain change is needed because of a new VOC, or if a strain change is advantageous to enhance a vaccine, even if not absolutely required.

• Additionally, robust data regarding the effectiveness of a prototype design against VOCs, and particularly against a more challenging new VOC is essential to establish appropriate non-inferiority vs superiority trial designs. This data is also required to establish the statistical criteria for GMTs and seroconversion in seronegative subjects if possible, as well as in seropositive subjects resulting from vaccination and infection.
Authorization Paths for Boosters and New Vaccines

• Homologues platforms with new VOC design booster vaccine:
  ➢ Again, the most appropriate assessment would be against circulating VOCs, not original strain.
  ➢ Non-inferiority of the VOC vaccine design against the prototype vaccine, for defined VOCs would establish a threshold for any specific VOC.
  ➢ The range of VOC breadth of coverage of the prototype against the VOC vaccine design for circulating VOC could also be an consideration for authorization.

• Heterologous platforms with new VOC design booster vaccine:
  ➢ As with homologues platform booster, also requires prior characterization as a new vaccine including the required safety data with immunobridging to an authorized vaccine.
Considerations for New COVID-19 Vaccine Authorizations

• HC considers all well-designed clinical trials (including placebo controlled disease endpoint designs), but will not require COVID-19 placebo trials in the current context.

• For new products without disease endpoint data, immunobridging against an authorised active comparator will be considered. HC, the UK’s MHRA and the other ACCESS Partners are aligned with the non-inferiority immunogenicity / superiority considerations outlined in the International Coalition of Medicines Regulatory Authorities (ICMRA) summary of their June 24, 2021 meeting*.

*www.icmra.info/drupal/en/covid-19/24june2021
New COVID-19 Vaccine Considerations Cont’d

- The ACCESS Partners are also aligned regarding cross-platform immunobridging. The use of WHO standards in neutralization studies is strongly recommended. In addition, applicants are expected to provide the following:
  - Relevant animal challenge studies to support proof of concept for new vaccines, with demonstration of effectiveness against variants of concern (VOCs) being strongly recommended;
  - Characterization of comparative immunogenicity profiles, including cell-mediated immunity;
  - Characterization of comparative \textit{in vitro} neutralization against VOCs;
  - Safety data in at least 3,000 adults of all ages with a median follow-up of at least two months post-final dose; and,
  - Post-authorization effectiveness studies.

Thank You

Questions?