Developing Scientifically Appropriate Immunobridging Criteria

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Outline

• Is immunobridging?
  ➢ a novel/controversial regulatory approach, or
  ➢ a well established regulatory pathway when scientifically justified.

• Why NAb are generally considered important but what of binding Ab CMI and innate immunity?

• It’s all about the comparator! What are “the right questions” to consider regarding active comparators in immunobridging clinical studies?

• Scientifically appropriate and rigours immunobridging criteria can expedite vaccines authorizations, including pathogen X (?)
Vaccine Authorizations Through Immunobridging

• Provided a vaccine has demonstrated efficacy in clinical endpoint trial, vaccine effectives can be inferred through immunobridging to:
  • Extend the indication to a different age or other demographic group
  • Authorize a new a formulation or antigen composition of the same vaccine
  • Authorized an alternate dose or dose schedule
  • Evaluate immune interference with concomitant administration with other vaccines
  • Serve as an active comparator to authorize new vaccines within the same platform and, if justified, across platform

• Non-COVID examples of within platform active comparator immunobridging authorizations include vaccines against: influenza virus (Flu), polio virus, and Hepatitis B virus

Key Message: Pre & post-COVID-19, in the absence of an agreed upon CoP with a defined serological/immunological threshold, immunobridging is an important tool.
NAb, Binding Ab, CMI and Innate Immunity

- Vaccines have been a “game changer” during the COVID-19 pandemic.
- However, with widespread infection, evolution of variants and increases in transmissibility there is a need for vaccines with greater breadth of protection (focus remains on severe disease) with enhanced deployability. Additionally, clinical end-point RCT are increasing challenging. Hence, immunobridging offers an important option, and is now included in WHO’s framework for COVID-19 vaccine EUL.


- While the clear weight of evidence supports NAb as a key CoP, what does that mean?
- Peak antibody titres correlate well with short-term protection from mild to moderate disease, but wanes. Whereas, protection against severe disease is more robust. This implies a role for CMI, and potentially even an early role with elements of innate immunity in influencing the establishment of more robust protection.
- While NAb and binding Ab can be well characterized, more robust assays to characterize CMI and innate immunity are needed.
It’s All About the Comparator
Its Demonstrated Efficacy and Characterization

- Vaccine platform (mRNA, live or inactivated virus, protein subunit etc.), single antigen vs multi-valent, adjuvant (?), will all influence the appropriateness (or not) of the choice of comparator for a candidate vaccine and the statistically appropriate considerations (e.g. NI vs Superiority for GMT in the NAb analyses).

- Key questions to considered should included:
  - What is the effectiveness or efficacy of the comparator vs. severe disease caused by circulating VOC, relative to TPP criteria?
  - Are the predicted/likely protective responses using the new vaccine likely to be similarly proportional to the humoral response vs. the comparator vaccine,
  - What is the breadth of antigenic composition of the new vaccine relative to the proposed comparator?

Vaccines that fall outside of these scenarios may be effective, but current consensus may not support evaluating their effectiveness without more rigorous placebo-controlled trials, although this becoming more difficult.
Scientifically Appropriate Immunobridging Criteria Can Expedite Vaccine Authorizations: What About Pathogen X?

• While immunobridging can be a useful approach to expedite new vaccine authorizations, confirmatory post-authorizations studies should be considered, and immunobridging may not be appropriate in all situations. In such cases traditional clinical end-point RCT or CHIM may be required, even if those are challenging.

• However, an essential requirement for immunobridging, which has been extremely challenging during the COVID-19 pandemic, is access to the most effective approved comparators.

  “Where feasible, comparisons should be made with vaccines with high efficacy against severe disease caused by circulating VoC, and we believe that manufacturers of high-efficacy vaccines should make their vaccines available for such comparisons.”

• Additionally, with Pathogen X for at least the first authorization, immunobridging may not be a suitable option.