Q&As developed by the COVAX Regulatory Advisory Group (RAG): Feb2021

Questions from the Enabling Science SWAT team

In the context of strain changes, two questions were brought to the RAG:

Background:

Immunogenicity/Efficacy in preclinical models for strain-change vaccines:

With the prototype vaccines, only basic immunogenicity studies were necessary prior to entering Phase I clinical trials. Challenge studies in relevant animal models were performed in parallel with the Phase I trials. We assume that the requirements for strain-change vaccines will not be more stringent, however, the immunogenicity studies will be more complex because they should include cross-reactivity against both the prototype and the variant strain(s). For multivalent vaccine candidates, the basic package of immunogenicity studies should also include an analysis of samples from animals vaccinated with each individual component alone compared to samples from animals vaccinated with the multivalent formulation to demonstrate non-interference of the multivalent formulation. We consider that these studies can be performed in mice and that there should not be a need to move into larger animals such as non-human primates (NHP) prior to entering the clinic.

Further immunogenicity studies coupled with challenge studies in relevant animal models (such as NHP) can be performed in parallel with clinical trials. The human population is now highly heterogenous and "messy" from a serological perspective, with individuals who are seropositive both from previous infection and from previous vaccination. Animal studies will afford a controlled environment in which to test immunogenicity elicited by various prime-boost combinations of prototype and strain-change vaccines, and to link the observed immunogenicity to any observed cross-protection from challenge from the various strains. Such studies could be particularly useful for evaluating the effect of pre-existing antibodies to the prototype virus (through vaccination or natural infection) on the development of variant strain-specific antibodies, a scenario that will be common in the "real world".

Question 1: Immunogenicity/Efficacy in preclinical models (i.e. mice studies prior to Ph1 and NHP studies in parallel to Ph1; mice studies to demonstrate non-interference of multivalent vaccine formulations).

Q1: Does the RAG agree with the above proposal (*reference is made to the pre-read material distributed prior to the RAG meeting*) that various combinations should be tested in relevant animal models, to reduce the number of combinations that would be required to be explored in clinical trials?

Feedback to Q1 (in the order it was provided):

- Generally, regulatory considerations were focusing on monovalent modification of a given vaccine either to replace the original vaccine or administration in a heterologous prime/boost strategy. The scenario of multivalent vaccines has, to date, had limited discussion and the views expressed were initial and preliminary thoughts.
- For multivalent vaccines, excluding interference would be important and may be best done by clinical assessment (cf experience with influenza quadrivalent vaccines).
- For monovalent vaccines, points mentioned under the previous topic ("SARS-CoV-2 Variants Scenario") were recalled. It was assumed that vaccine manufacturers would have retained serum samples from individuals vaccinated with prototypes which could be tested/compared to new variant vaccines, to avoid the challenges of vaccinating with a prototype that may no longer work against the new variant.
- It is difficult to transpose non-interference data from mice to NHP and/or humans (in particular with mRNA vaccines). As a result, nonclinical studies are valid in the exploratory space, though clinical immunological bridging data would be expected to be more relevant.
- It was also questioned as to whether multivalent vaccines were an immediate priority given that there is limited data as to whether a variant strain would replace the current circulating SARS CoV-2 strains or whether they would co-exist.
- It was acknowledged that discussion about multivalent vaccines should consider the potential of antigenic competition (pneumococcal as well as influenza vaccines were mentioned as examples of assessment of antigenic competition).

Background:

Q2: Regarding the key assays: wild-type and pseudo type neutralization assays, and antibody-binding assays, does the RAG agree that these assays do not need to be qualified prior to phase 1 studies?

- Clarification was asked about the term "prior to Phase 1 studies", since clinical immunogenicity bridging studies assessing variants are not considered to be Phase 1 studies.
- The RAG agreed assays should be qualified and sufficiently controlled to be able to draw conclusions and take decisions. Qualification of antibodies used to evaluate neutralizing titres in the assays would be expected, in order to have certainty about the results being measured with the assays.
- Not having a qualified assay from the beginning of the trial could make data difficult to interpret and could impact regulatory review.

Question from the Clinical Development and Operations SWAT team

It is anticipated that enrolment into placebo-controlled efficacy trials will become more challenging. In some countries a sizeable portion of the population has been vaccinated. Gathering data from placebo-controlled arms will become more difficult as patients drop out to be vaccinated. It is also likely that the duration of follow-up will have to be increased in order to achieve the appropriate number of clinical endpoints. This is creating significant challenges for "wave 2" vaccine development.

The clinical SWAT team believe that there is sufficient immunological data to consider a registration strategy where licensure is based on neutralising antibody data from a randomized non-inferiority immunologic study versus a vaccine which has previously demonstrated clinical efficacy. If successful, emergency use or licensure could be granted to a sponsor with the requirement to demonstrate effectiveness as a post licensure commitment. This immunologic comparison would be valid for assessment versus a vaccine based on a similar manufacturing platform, or a vaccine which generates a humoral and cellular immune response profile of similar characteristics.

Four questions were brought to the RAG in relation to the topic described above:

Q1:

Can emergency use or licensure be supported for a new COVID-19 vaccine through demonstration of non-inferior immune response as measured by wild-type neutralization GMTs at 2-4 weeks post completion of vaccination series, in a randomized trial compared against a COVID-19 vaccine which has demonstrated clinical efficacy, provided an adequate effectiveness study is conducted post licensure.

a. As a comparison to a vaccine based on a similar manufacturing platform? or

b. As a comparison to a vaccine which induces a comparable humoral and cellular immune response profile

Q2:

Are there specific concerns with this approach, or additional data needed to de-risk?

Q3:

What would you consider to be the appropriate NI margin?

Q4:

Would GMT be the acceptable readout?

It was noted that the RAG cannot give clear answers at this time because discussions and learnings are ongoing, however, this is a good framework that developers can follow to begin discussions with regulators.

Feedback to Q1 to Q4:

- This topic is regularly being discussed within agencies
- It was stressed that developers should still consider efficacy studies with clinical disease endpoints.
- The challenges of conducting placebo-controlled studies were acknowledged and other clinical designs might be considered.

- A recently available publication on clinical non-inferiority studies with active comparators suggests a two to three-fold longer follow up period being required compared to placebo-controlled trials ("COVID-19 vaccine trials: The use of active controls and non-inferiority studies" https://journals.sagepub.com/doi/pdf/10.1177/1740774520988244). This raised a question about feasibility of conducting such studies.
- The possibility to explore human challenge studies was also mentioned.
- Acceptability of non-inferiority immunological endpoint approaches will likely be decided on a case-driven discussion and would be based on the data and rationale proposed by developers, including e.g. broad immunological data set comprising both antibodies and CMI responses and whether the comparison occurs within a platform or not.
- Developers should build robust rationale for their approach and engage in scientific advice discussions with regulators. Future acceptability would be dependent on a greater understanding of CoP / immune markers. In the case that immunological data are accepted as the primary data for authorization, confirmatory effectiveness studies post-authorization would be required.
- The modality of immune response profiles is considered important when thinking about immunological comparisons across vaccines. This should be assessed on a case-by-case basis.
- One RAG member highlighted that vaccines may be approved in certain countries and not in others and in some countries the selection of a comparator may also be driven by local regulatory requirements. Therefore, the choice of comparator to support a global trial may be complex. Another element was raised regarding vaccines potentially approved with low efficacy, e.g., close to 50% and these being selected for use as a comparator. In the event that such a vaccine were to be used as a comparator and the new vaccine demonstrated efficacy just above the lower bound of the non-inferiority margin then the new vaccines might be considered as only having marginal efficacy. Diverging opinions within the RAG were noted, with the choice of a vaccine comparator preferably being based on science vs. a regulatory framework. It was highlighted that agreement at international level as to which comparators are appropriate to consider would be beneficial. Lastly, it was noted that crisis such as the COVID-19 pandemic may offer an opportunity to adopt flexibility with local regulatory requirements and ensure there is allowance for evolving science to be the driver behind which comparator should be used in a study.
- Non-inferiority margins should be discussed in the context of the assays used. Read-outs to consider should not focus solely on neutralizing antibodies GMTs but consider other parameters too, such as seroconversion rates. The use of WHO international standards in clinical assays as a means to allow comparison of data from different developers was considered important.
- A suggestion to include two comparators within an immunological study (one within the same platform and the other across platforms) as a way to de-risk the development programme was discussed. Hesitation was noted as this approach could result in much longer and more complex studies. Instead, it was suggested this could be part of exploratory nonclinical studies.
- The conduct of small placebo-controlled trials with lower confidence bounds was brought into the discussion as an intermediate approach between large efficacy studies and immunological comparison studies. Given that such studies would be statistically weak, the value of data gathered would be limited.