APPENDIX TO

REVISED Considerations for Evaluation of COVID-19 Vaccines for Prequalification or Emergency Use Listing

Considerations for evaluation of modified COVID-19 vaccines

Points to consider for manufacturers of COVID-19 vaccines

version 30 March 2022
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Introduction

This APPENDIX, originally written as an ADDENDUM (published on 12 March 2021) to the document “Considerations for evaluation of modified COVID-19 vaccines: Points to consider for manufacturers of COVID-19 vaccines” (published on 20 November 2020), has been updated and incorporated into this revised version of the latter.

In November 2020, the World Health Organization (WHO) published a guidance that provides advice to manufacturers on both the process and the criteria that will be used by WHO to evaluate COVID-19 vaccines that are submitted either for prequalification (PQ) or for Emergency Use Listing (EUL). Since then, several preliminary efficacy estimates of vaccines against SARS-CoV-2 infection have been released to the public and many of these vaccines have received conditional approval or authorization by at least one National Regulatory Authority (NRA). WHO, in collaboration with several National Regulatory Authorities (NRAs), have listed four of these vaccines under the WHO EUL procedure as of 30 March 2022.

SARS-CoV-2 variants of concern (VOC), with potential to negatively impact mortality and morbidity and escape vaccine induced immunity, have been identified since the last quarter of 2020 and more are likely to appear in future. Data on SARS-CoV-2 VOCs indicate that some variants are less well neutralized by antibodies developed following vaccination with vaccines produced against the original SARS-CoV-2 virus and may require modified vaccines to counter these VOCs. To facilitate regulatory review and listing of these modified COVID-19 vaccines, this addendum was developed to ensure scientifically sound, ethically acceptable, efficient, prompt and reliable evaluation of modified monovalent COVID-19 vaccines. This document is also applicable to the modified component of a bi- or multi-valent vaccine.

This document should be read in conjunction with the revised guidance “Consideration for evaluation of COVID-19 vaccines: Points to consider for manufactures of COVID-19 vaccines, version 30 March 2022”. All requirements in the original guidance and other applicable references, including the guidelines on the nonclinical evaluation of vaccines (TRS 927, Annex

1 Consideration for evaluation of COVID-19 vaccines: Points to consider for manufacturers of COVID-19 vaccines, version 25 November 2020
2 WHO Working definitions of SARS-CoV-2 Variants of Interest and Variants of Concern https://www.who.int/publications/m/item/covid-19-weekly-epidemiological-update
1) and clinical evaluation of vaccines (TRS 1004, Annex 9), remain applicable to modified COVID-19 vaccines.

WHO has been in consultation with NRAs to ensure a harmonized approach and alignment in the requirements for evaluation of the modified COVID-19 vaccines.

This is a living document subject to changes as new data become available. In this document:

- Original SARS-CoV-2 virus refers to the virus based on which the prototype vaccine was developed.
- SARS-CoV-2 VOC refers to virus to which the modified vaccine is targeted.
- Prototype COVID-19 vaccine refers to the vaccine based on the original SARS-CoV-2 virus.
- Modified COVID-19 vaccine refers to the vaccine against the SARS-CoV-2 VOC for which the change is only in the virus strain without changes in the manufacturing process, controls and the facilities for vaccine production. Modified COVID-19 vaccines can be mono-, bi- or multi-valent, which is a combination vaccine targeting the original SARS-CoV-2 strain and a new VOC.

Scope

This guidance applies to the evaluation of modified versions of monovalent vaccines (or modified components of bi- or multi-valent vaccines), in accordance with WHO recommendations to address SARS CoV-2 variants, that have been listed, or are being assessed, under the WHO EUL procedure.

Important background to this addendum

- Due to the increasing availability of vaccines against SARS-CoV-2 infection worldwide, it is increasingly difficult to do a placebo-controlled trial with clinical endpoints that meets the WHO criteria as specified in the guidance document “Expert Consultation on the use of Placebos in Vaccine Trial”.
- Although infection with SARS-CoV-2 virus induces both antibody-mediated and cell mediated immune responses, available data suggest that neutralizing antibodies to the spike protein which are induced by either natural infection or following vaccination are important for protection.

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3 Expert consultation on the use of placebos in vaccine trial, 2013: https://apps.who.int/iris/bitstream/handle/10665/94056/9789241506250_eng.pdf?sequence=1
6 Addetia, A. et al. Neutralizing Antibodies Correlate with Protection from SARS-CoV-2 in Humans during a Fishery Vessel Outbreak with a High Attack Rate. JCM (2020)
8 Voysey et al. 2021. Single dose administration, and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine. Lancet pre-print. doi: https://jssm.com/abstract=3777268
Current evidence suggests that a relationship exists between elevated neutralizing antibody titers and efficacy against original SARS-CoV-2 (D614G) strains and protective immunity may be inferred from neutralizing antibodies assays. It is currently assumed that similar relationship exists for the SARS-CoV-2 variants.

The correlate of protection or defined threshold level of immune response that predicts protection against SARS-CoV-2 infection have not been established. Consequently, the degree of seroconversion, or geometric mean antibody titre, that confer protection are not known.

WHO has developed an integrated approach to monitoring and assessing SARS-CoV-2 VOCs and their impact on public health interventions, including public health and social measures, vaccines, diagnostics, and therapeutics and will be making recommendations for strain change(s), if needed, to guide decisions to any COVID19 vaccine modifications.

COVID-19 vaccines and vaccine candidates are at various levels of development.

1. Vaccines that have received WHO EUL listing: The document provides guidance for evaluation of modified vaccine candidates produced by the same manufacturing process and site as the original, prototype COVID-19 vaccine. It does not provide guidance for comparing modified COVID-19 vaccine candidates with other vaccines from either the same or different vaccine platforms. The Guideline is for monovalent modified candidate vaccines (or modified components of bi- or multi-valent vaccines).

2. Bi- or multi-valent vaccines will require immunogenicity studies to define the appropriate dose for each component and to investigate immune interference between them. In addition, the reactogenicity of the combination should be evaluated and compared to the monovalent vaccines.

3. Vaccine candidates that are in late-stage phase III trials that may or may not have released preliminary efficacy results: Manufacturers are encouraged to provide data that show the level of neutralizing antibodies the vaccine induces against SARS-CoV-2 VOC.

4. Vaccine candidates based on original SARS-CoV-2 virus that are in phase I or phase II trials that may or may not have released immunogenicity and safety data: Manufacturers should include testing SARS-CoV-2 VOC during the clinical development. Advice on the use of active controls and non-inferiority study designs has been published.

5. Vaccine candidates that are in or will soon be in non-clinical studies: Manufacturers should evaluate protection against SARS-CoV-2 VOC in the design of their vaccine candidates.

Additional Non-clinical data

Non-clinical studies are encouraged in the evaluation of emerging SARS-CoV-2 variants. Data on the impact of the antigen change to the immune response may be required. This data should be generated using validated methods.

In general, it might not be necessary to conduct repeat dose toxicity study or development and reproductive toxicity studies with the modified COVID-19 vaccine as this may be inferred from the prototype vaccine data. However, this decision should be supported with a sound scientific basis.

https://journals.sagepub.com/doi/pdf/10.1177/1740774520988244
Bio/Immunological markers to be evaluated should include the relative levels of neutralizing vs non-neutralizing antibodies, antibody avidity, T-cell response profile (Th1/Th2) and characterization of lung histopathology. Studies should include an evaluation of humoral, cellular, and functional immune responses, as appropriate to each modified COVID-19 vaccine candidate. Use of isotype-specific enzyme linked immunosorbent assays (ELISA) should be considered to characterize the humoral response. Evaluation of cellular responses should include the examination of CD8+ and CD4+ T cell responses using sensitive and specific assays. Data from the prototype vaccine may be acceptable as long as satisfactory rationale is provided.

In a situation where the efficacy data from the prototype COVID-19 vaccine is between 50 - 60%, non-clinical data from animal models that received the prototype vaccine and the modified vaccine and subsequently challenged with wild type viruses represented in the modified vaccine will be especially useful. Data on animal challenge studies are critical for the evaluation of vaccines based on immunobridging studies. Immunization/challenge data from animal models may also be considered in situations where clinical immunogenicity studies are difficult (see below) or if there are ambiguities in interpretation of clinical immunogenicity data. The manufacturer should discuss this with the NRA and with WHO PQT before conducting such studies.

Clinical Assessment

Inference of the effectiveness should be supported by conducting clinical immunogenicity studies of the modified COVID-19 vaccine against the SARS-CoV-2 VOC. The studies should compare, in a head-to-head study, the immune response induced by the modified COVID-19 vaccine against the SARS-CoV-2 VOC, to that induced by the prototype vaccine against the original SARS-CoV-2 virus. The reference prototype vaccine should have demonstrated efficacy in a Good Clinical Practice compliant trial. Where possible, this comparative study should be with the commercial scale lots of the modified vaccine.

Study Design:

This should be a non-inferiority study that compares the immune response induced by the modified COVID-19 vaccine to that by the prototype COVID-19 vaccine. The primary analysis should assess the neutralizing antibodies elicited by the modified COVID-19 vaccine against SARS-CoV-2 VOC strains compared to the neutralizing antibodies elicited by the prototype COVID-19 vaccine against the original virus upon which the prototype vaccine was based.

The data should as much as possible be generated in a naïve population. However, considering the widespread infection and current effort to vaccinate as many people as possible, data from a non-naïve population can be generated if there is difficulty in identifying a naïve population. In both instances, an acceptable response should be appropriately defined and justified (see TRS 1004, Annex 9). Studies that compared the immune response from the modified vaccine with historical data from the prototype vaccine may not be acceptable. The exception to this is when
a study comparing both vaccine types (prototype and modified) are not ethical because the prototype would be considered less effective due to a preponderance within the community of the SARS-CoV-2 variant(s). In such a situation the challenge study data from animal models should also be considered. Human challenge studies may be helpful if feasible and accepted by relevant ethics committee.

The margin of non-inferiority should be -10% and the lower bound of the 95% confidence interval around the geometric mean (GMT) ratio should be at least 0.67. Reverse distribution curves should also be provided. If the prototype vaccine efficacy result was less than 60%, a stricter non-inferiority margin should be used. This is to reduce the risk of listing/approving a modified vaccine with a lower vaccine efficacy than stipulated in the WHO Target Product Profile (TPP).

Additional analyses should evaluate the immune responses elicited by the modified vaccine versus the prototype vaccine against the virus upon which the prototype vaccine was based, as well as the immune responses elicited by the modified vaccine versus the prototype vaccine against the variant(s) of interest.

Bridging studies for the modified COVID-19 vaccine may be conducted in the 18-55 years age group, with extrapolation of results to other age groups for which the prototype vaccine has efficacy data.

**Booster study**

Data from booster studies in which the prototype vaccine and modified vaccine COVID-19 vaccine are administered to people who previously received the prototype COVID-19 vaccine should be provided. The primary non-inferiority (or superiority) immunogenicity analysis should assess the neutralizing antibodies elicited by the modified COVID-19 vaccine booster against SARS-CoV-2 VOC compared to the prototype COVID-19 vaccine schedule against the virus that the prototype vaccine was derived from.

Seroconversion, non-inferiority margin and other analysis consideration are as described earlier. Analogous orientation should be followed in the case of booster with a heterologous vaccine.

**Assay**

The functional activity of immune responses should be evaluated *in vitro* in neutralization assays using either wild-type variant virus or pseudovirus microneutralization. The assays used for immunogenicity evaluation should be validated for their intended purpose, calibrated against WHO International Standards (IS), and antibody titres should be expressed in International Units (IU).

The Expert Committee on Biological Standardization (ECBS) established the first WHO International Standard Anti-SARS-CoV-2 Immunoglobulin (Human) with assigned unit of 250 IU/ampoule (neutralizing antibody activity). This is available from the National Institute for Biological Standards and Control, WHO Collaborating Centre and International Laboratory for Biological Standards, in the United Kingdom upon request.

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Safety

The general safety evaluation should be no different than for other preventive vaccines.

- Solicited local and systemic adverse events for at least 7 days after each study vaccination in an adequate number of study participants to characterize reactogenicity.
- Unsolicited adverse events in all study participants for at least 28 days after each study vaccination.
- Serious adverse events in all study participants for the duration of the study.
- Subgroup analyses of safety stratified by prior infection status at trial enrolment should be performed.

Longer safety monitoring may be needed for certain vaccine platforms (e.g., those that include novel adjuvants). If there is any safety concern or signals identified following the administration of the modified vaccine, a large safety study might be necessary.

Reports should include adverse events among study subjects occurring at least 14 days after the last dose is administered in modified COVID-19 vaccine compared to prototype vaccines recipients.

Risk Management Plan

Since the modified COVID-19 vaccine will be listed based on immune response, the manufacturer should propose a plan to provide effectiveness data on the variant COVID-19 vaccine.

Chemistry, Manufacturing and Quality Controls

All the recommendations specified in the Revised guidance “Consideration for evaluation of COVID-19 vaccines,” version 30 March 2022 apply.

It is expected that facilities for production, manufacturing process and control for the modified COVID-19 vaccine will be identical to that used for the prototype vaccine.

In addition, data on the control of materials, the platform (i.e., characterization of the virus seed/construct), potency data and stability data should be provided. There should be data on control of critical steps and intermediates for both the drug substance and the drug product, process validation, analytical procedures and their validation (tests specific for the new variant/strain) and batch analysis results.

A full package of phenotypic and genotypic characterization studies of parent, master and working virus seeds of new variants should be provided. Data of sequencing of the working virus seed (WVS) on the Nextstrain phylogenetic tree to assess its “distance” from prototype in terms of number of mutations, for the sequences of the antigenic sites (protein S, protein N) should be provided. Also confirmed genome sequencing should be maintained throughout production steps and product shelf life. The genome sequence should be comparable to the published reference sequence of SARS-CoV-2 VOC.

It should be noted that the immunogenicity of inactivated vaccines may be affected by the quantity and length of residual RNA after inactivation, and the evidence of validation (of inactivation) must be provided. Good quality control is crucial to monitor the specification to ensure consistency between batches and this should be evident in the documentation.

In the development of bi- or multi-valent vaccines, further considerations should be given to assure the quality of the individual active substances at release and up to the end of shelf life.
This would primarily relate to the manufacturing and control of the finished product (e.g., the control of total level of impurities and the validity of the analytical procedures to test vaccines containing different variant strains). The specifications would need to be adapted due to the additional variants. Pharmaceutical development studies and a change to the finished product control strategy in terms of formulation would be required. The requirements for batch analysis data and process validation data are also considered to be higher when moving from a monovalent parent vaccine to a multivalent variant vaccine.

Due to the complexities involved and additional data that need to be generated, manufacturers planning to the development of a multi-valent vaccine are encouraged to discussed this with the relevant NRA and WHO PQ.