CONSIDERATIONS FOR EVALUATION OF COVID19 VACCINES

Points to consider for manufacturers of COVID19 vaccines

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Contents

1. EXECUTIVE SUMMARY

This document provides advice to manufacturers on both the process and also the criteria that will be used by the World Health Organization (WHO) to evaluate COVID-19 vaccines that are submitted either for prequalification (PQ) or for Emergency Use Listing (EUL). The current status of development of a candidate Covid-19 vaccine, the extent of the available quality, safety and efficacy data and regulatory approvals by relevant NRAs will guide WHO's decision on which pathway (PQ or EUL) to follow for each vaccine.

The document is not to be read as a standalone document. Other relevant documents, as cited, must also be consulted.

The submission and review processes are described. Only vaccines that have undergone phase IIb or phase III studies and have received authorization from a reference NRA should be submitted for consideration. Criteria that will be used to assess clinical trial design, endpoints, and statistical criteria are described. Specific data that should be submitted to answer programmatically relevant questions are outlined. Manufacturing, quality control and labelling requirements are summarized, as are non-clinical data to address the potential for vaccine-associated enhanced disease. Post-authorization commitments are specified.

WHO encourages early, pre-submission discussions with interested manufacturers.

2. INTRODUCTION

The United Nations Children's Fund (UNICEF) and other United Nations (UN) agencies take into consideration advice provided by the World Health Organization (WHO), through its Department of Regulation and Prequalification (RPQ), on the acceptability, in principle, of vaccines considered for purchase by such agencies; this is known as vaccine prequalification (PQ). In addition WHO has developed a time limited Emergency Use Listing Procedure (EUL) to expedite the availability of medical products needed in public health emergency situations, to assist interested UN procurement agencies and Member States on the acceptability for use of specific products in the context of a public health emergency, based on an essential set of available quality, safety, and efficacy/immunogenicity/ performance data[1]. Both procedures include, for each product, the evaluation of data submitted contained in the Common Technical Document (CTD) format.

The review of the quality, safety and efficacy/immunogenicity data is performed by WHO experts. Their recommendations are taken into account by WHO in the decision-making process for prequalification or EUL of each individual product.

The WHO evaluation of vaccines either for EUL or PQ, considers the suitability for use in Low- and Middle-Income Countries (LMICs). In their reviews WHO focuses on information that may not be part of the NRA approval process, although in practice they also do at least a verification

[1] https://www.who.int/immunization_standards/vaccine_quality/EUL/en/

of what is expected to have been evaluated by the NRA. Any vaccine submitted for WHO assessment should have been authorized by the reference NRA (emergency use approval or equivalent or standard licensure/marketing authorization).

This document should be read in conjunction with the following:

1. "Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies", WHO Technical Report Series 978, Annex 6, 2013[2]

2. WHO EUL document[3]

3. "Guidelines on clinical evaluation of vaccines: regulatory expectations", WHO Technical Report Series 1004, Annex 9, 2017[4]

4. COVAX SAGE Compendium of Covid-19 vaccine research questions[5]

5. "Guidelines for assuring the quality, safety, and efficacy of plasmid DNA vaccines" adopted by the Seventy-first Meeting of the World Health Organization Expert Committee on Biological Standardization, 24–28August 2020.[6]

6. "Points to Consider for assuring the quality, safety and efficacy of RNA vaccines"[7] (currently under development).

Based on the current status of development of Covid-19 vaccines candidate, the extent of the available quality, safety and efficacy data and regulatory approvals by relevant NRAs, WHO shall follow either EUL process or Prequalification. Once a product has been listed under the EUL procedure, the development of the product must continue to completion for marketing authorization and be submitted to WHO for prequalification.

3. SUBMISSION AND REVIEW PROCESS

3.1. CLINICAL ASSESSMENT

3.1.1. Format and content of an application

The format of the application should follow the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) CTD format. Refer to "Vaccine Prequalification Dossier"[8]

[2] http://www.who.int/immunization_standards/vaccine_quality/TRS_978_61st_report_Annex_6_PQ_vaccine_procedure.pdf?ua=1

[3] https://www.who.int/medicines/regulation/prequalification/prequal-vaccines/EUL_PQ_Vaccines/en/

[4] http://www.who.int/biologicals/expert_committee/WHO_TRS_1004_web_Annex_9.pdf

[5] COVAX SAGE Compendium of Covid-19 vaccine research questions https://www.who.int/immunization/policy/position_papers/en/

[6] https://www.who.int/publications/m/item/DNA-post-ECBS-1-sept-2020

[7] currently under development and to be published at https://www.who.int/biologicals

[8] http://www.who.int/immunization_standards/vaccine_quality/VaccinePQ-dossier_Dec2017.pdf?ua=1

3.1.2. Screening of applications

The CTD of a vaccine submitted for evaluation is expected to have complete information to support the efficacy, immunogenicity and safety of that product, and evidence that such information is adequate for a wide use of the vaccine if prequalified or listed.

Queries may be sent to the applicant at this stage, and the acceptance of the application for review will be conditional to satisfactory answers. See specific data requirement below.

3.1.3. Requirement for additional non-clinical Information

The CTD requires the presentation of a summary table of non-clinical studies that would have been assessed by the NRA of reference. Additional information on non-clinical studies can be requested by the clinical reviewers whenever necessary, and if this is anticipated by the applicant such information may be included in the application. If novel adjuvants are used, relevant non-clinical data must be submitted.

Data from studies in animal models of certain vaccine constructs against other coronaviruses (SARS-CoV and MERS-CoV) have raised concerns of a theoretical risk for COVID-19 vaccine-associated enhanced respiratory disease (ERD). Current knowledge and understanding of the potential risk of COVID-19 vaccine associated ERD is limited, as is understanding of the value of available animal models in predicting the likelihood of such occurrence in humans. Nevertheless, studies in animal models (e.g., rodents and non-human primates) are considered important to address the potential for vaccine-associated ERD.

Studies should include an evaluation of humoral, cellular, and functional immune responses, as appropriate to each of the included COVID-19 antigens. Use of antigen-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. The functional activity of immune responses should be evaluated in vitro in neutralization assays using either wild-type virus or pseudovirus microneutralization. The assays used for immunogenicity evaluation should be demonstrated to be suitable for their intended purpose.

3.1.4. Clinical development programme

The applicant should provide in the CTD a tabulated summary of the clinical development programme in one or more tables.

3.1.5. Requirement for the protocols of clinical trials that support application

The applicant must provide the English version of the protocols of the clinical trials supporting the application. The protocols should be the final approved versions, incorporating all amendments.

3.1.6. Evidence of Ethics Committee approval of clinical trials

Evidence of approval of the clinical trials by competent Ethics Committees, as well as information about their contact details, are expected to be included in the CTD.

3.1.7. Evidence for Good Clinical Practices (GCP) conduct of each trial

In the absence of a certificate of GCP compliance from the responsible NRA, applicants should provide evidence of GCP compliance for each trial. This might include evidence of the monitoring of the trial conduct by the sponsor (or contract research organization), audits by the sponsor, available NRA inspection reports or Data and Safety Monitoring Board (DSMB) reports.

3.1.8. Evidence for registration of each clinical trial

Each clinical trial that supports an application must have been registered in a registry that is included in the WHO International Clinical Trials Registry platform. The name of the registry and the registry number must be provided. If this is not possible the reason(s) should be provided.

3.1.9. Clinical trial design[9] [10]

- Phase IIB/III efficacy trials should be randomized, double-blinded, and placebo controlled.
  An individually randomized controlled trial with 1:1 randomization between vaccine and placebo groups is usually the most efficient study design for demonstrating vaccine efficacy. Other types of randomization, such as cluster randomization, may be acceptable if there is evidence that potential biases have been avoided.

- Protocols for adaptive trials should include pre-specified criteria for adding or removing vaccine candidates or dosing regimens, and protocols for seamless trials should include pre-specified criteria (e.g., safety and immunogenicity data) for advancing from one phase of the study to the next.

- Follow-up of study participants for COVID-19 outcomes (in particular for severe COVID-19 disease manifestations) should continue as long as feasible, ideally at least one to two years, to assess duration of protection and potential for vaccine-associated Enhanced Respiratory Disease (ERD) as immune responses to the vaccine wane.

- Efficacy trials should include contingency plans for continued follow up and analysis of safety and effectiveness outcomes in the event that a safe and effective vaccine becomes available and the study is stopped (e.g., as demonstrated in a planned interim analysis or as demonstrated in another clinical trial). In that case, discussion with the WHO may be necessary to address ethical arguments to break the blind and offer vaccine to placebo recipients.

3.1.10. Statistical Considerations[11] [12] [13]

- To ensure that a widely deployed COVID-19 vaccine is effective, the primary efficacy endpoint point estimate for a placebo-controlled efficacy trial should be at least 50%, and the statistical success criterion should be that the lower bound of the appropriately alpha-

[9] FDA Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry June 2020.

[10] Guidelines on clinical evaluation of vaccines: regulatory expectations", WHO Technical Report Series 1004, Annex 9, 2017

[11] FDA Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry June 2020

[12] WHO Target Product Profiles (TPP) for COVID-19 Vaccines (Version 3 - 29 April 2020)

[13] Guidelines on clinical evaluation of vaccines: regulatory expectations", WHO Technical Report Series 1004, Annex 9, 2017

adjusted confidence interval around the primary efficacy endpoint point estimate is >30%.

- The same statistical success criterion should be used for any interim analysis designed for early detection of efficacy.

- A lower bound ≤30% but >0% may be acceptable as a statistical success criterion for a secondary efficacy endpoint, provided that secondary endpoint hypothesis testing is dependent on success on the primary endpoint.

- For non-inferiority comparison to a COVID-19 vaccine already proven to be effective, the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary relative efficacy point estimate is >-10%.

- For each vaccine candidate, appropriate statistical methods should be used to control type 1 error for hypothesis testing on multiple endpoints and/or interim efficacy analyses.

- Phase IIb/III studies should include interim analyses to assess risk of vaccine-associated ERD and futility.

- Study sample sizes and timing of interim analyses should be based on the statistical success criteria for primary and secondary (if applicable) efficacy analyses and realistic, data-driven estimates of vaccine efficacy and incidence of COVID-19 (or SARS-CoV-2 infection) for the populations and locales in which the trial will be conducted.

3.1.11. Clinical trial end-point assays - relevance, validation and accreditation

In some clinical trials the assays used to determine immunogenicity end-points (including thresholds for seroconversion) have no evidence of relevance to the efficacy of the vaccine in question (e.g. specificity), and there is often no evidence of assay validation or standardization, or of the competence of the laboratory to conduct these tests.

The serological correlate of protection used in the analyses must be justified and supported with best scientific evidence available. Evidence should be provided of end- point immunogenicity assay relevance and standardization. Assay results should be reported in international units wherever possible. The laboratory should be identified, and evidence of competence or accreditation to conduct these assays should be provided.

3.1.12. Vaccine lots used in clinical studies and lot-to-lot consistency studies

Consistency of manufacturing for the vaccine candidate lots used in clinical trials should be demonstrated and well documented. Ideally, at least three lots with the same formulation intended for marketing are used in the late stages of the clinical development programme. However, a formal lot-to-lot consistency clinical study may be considered only on a case-by-case basis, in particular, when assessing vaccine formulations with inherent variability.

3.1.13. Subject exposure to a new vaccine in clinical trials

For assessment of safety and immunogenicity the results from an adequate number of subjects, exposed to the vaccine, and monitored during comparative clinical trials are expected to be provided for prequalification review. The sample of subjects should be enough to give the study a minimum of 80% statistical power to detect adverse events of concern that may occur at about 1:1000 incidence. The vaccine characteristics, the population under study and the study design should be considered to determine the number of the subjects evaluated in clinical trials. This needs not be a single clinical trial but could represent cumulative exposure across all clinical studies provided that the vaccine used in these studies is similar to and representative of the final formulation to be marketed. In cases where vaccines had been authorized by NRAs based on small sample sizes and where there is insufficient supporting safety data, this needs to be discussed before submission.

3.1.14. Follow-up in clinical trials

The expectation is that the follow-up of study participants for COVID-19 outcomes (in particular, for severe COVID-19 disease manifestations) should continue as long as feasible, at least one to two years, to assess duration of protection and potential for vaccine-associated ERD as immune responses to the vaccine wane. This follow up should be active and not reliant on spontaneous reports. For efficacy and immunogenicity assessment longer follow-up, of at least one year, may be expected depending on the clinical endpoint requirements.

3.1.15. Requirement for a risk management plan as part of the CTD

Risk management plans, including pharmacovigilance plans, are part of modern risk management strategies required for vaccines. This is particularly relevant in COVID 19 where more knowledge is still being accumulated. A Pharmacovigilance plan taking into consideration where the vaccine is likely to be used if listed/prequalified, is required as an essential part of the EUL/PQ submission. This plan should include actions designed to address all important identified and potential risks.

3.1.16. Specific data should be submitted to answer the following questions

Only vaccines that have undergone phase IIb or phase III studies and have received authorization from a reference NRA should be submitted for consideration.

Efficacy:

- Is there evidence of clinical efficacy against hospitalizations, severe disease and/or mild symptomatic disease in non-older adults (including women of child-bearing potential), older adults, elderly, children, pregnant and breast-feeding women, and/or specific co-morbidity risk groups measured as Vaccine Efficacy (in % and 95%CI)? WHO Target Product Profiles[14] should serve as a guide.

- Is there evidence of reducing vaccine-preventable disease incidence?

[14] WHO Target Product Profiles (TPP) for COVID-19 Vaccines (Version 3 - 29 April 2020)

Immunogenicity:

- Is there evidence of induction of neutralizing antibody after 1 / 2 doses in the different groups (older adults, elderly, children, pregnant and breast-feeding women) and of immunoassay-measured antibodies? Likewise measured as concentrations/titres of antibodies or seroconversion rates vs pre-vaccination values or, if a correlate is established, seroprotection rates? This evidence will be of enhanced value once serological correlates of protection become available.

- What is the available evidence concerning functional antibody assays /neutralizing antibody assays, their standardization and use in phase 1-3 trials? Have one or more of the described assays been correlated to clinical protection?

- What is the available evidence on immunoassays being used to assess responses to vaccines? Have any of these assays been correlated to functional/neutralization assays or to clinical protection?

Duration of protection:

- Is there evidence of persistence of protective / neutralizing / immunoassay-measured antibodies over time (e.g. 6, 12 months) after completion of 1 / 2 dose course of immunization in the different groups (older adults, elderly, children, pregnant and breast-feeding women)? This can be measured as decay in antibody titers over time.

Indirect Effect:

- Is there evidence of impact of immunization on rates of detection (binary endpoint) or viral load (continuous variable - increase PCR Ct values), other measures of infectiousness (e.g. subgenomic viral RNA) or duration of shedding of SARS CoV2 in active surveillance by respiratory tract sampling in study subjects and controls?

- Is there evidence of reduction in new SARS-CoV-2 infections in contacts of vaccinated as compared to control study subjects who become infected? (This could be answered by an adjunctive protocol to large RCTs, comparing onward transmission to household contacts of subjects and controls who are found to be infected on active surveillance).

- Is there evidence of impact of immunization on rates of onward transmission in immunized groups? (This could theoretically be answered by cluster randomized studies focusing on infection rates in un-immunized members of immunized clusters - if logistical and ethical challenges of undertaking such trials could be overcome)

Target populations:

- How to extrapolate to potential target populations (age, ethnicities, co-morbidities) for whom there may be insufficient data (effectiveness, safety).

Vaccine Safety data:

- Is there evidence on rates of local and generalized expected AEs (sore arms, fever, headaches, malaise etc.) using standardized definitions and ascertainment methods?
- Is there evidence of absence of enhanced disease in vaccine recipients subsequently exposed to the virus.
- Is there evidence of any SUSARs (severe unexpected serious adverse reactions) including but not restricted to cases of (or absence of cases of) inflammatory disease or other manifestations following vaccination (e.g. mimicking pediatric multisystem inflammatory syndrome and toxic-shock - PMIS-TS)?
- Is there data on safety in pregnant women?
- Is there data on safety in lactating mothers?

Manufacturers should provide safety data as indicated in the list of adverse events of special interest proposed by WHO GACVS.[15]

Benefit Risk Assessment Report.

A detailed review of available data and objective Benefit and Risk assessment of the vaccine should be provided at the time of submission.

3.1.17. Minimum clinical criteria for EUL assessment

For clarity, the following information must be part of the dossier for EUL application. However, the totality of the available scientific evidence relevant to the product (the preclinical and human clinical study data) will be considered.

Results from both final report and pre specified interim reports are acceptable

Results for a given vaccine will be reported when the study reaches a monitoring boundary. Interim analyses should be timed considering the potential of such analyses to meet the criteria noted below.

After this report, study subjects will continue to be followed for additional endpoints as additional safety and efficacy data is required. Efficacy against the secondary endpoint of severe disease should be reported at the time that primary endpoint analyses are reported.

Efficacy should be evaluated by accumulating end points at least two weeks after full schedule administered. and for at least 3 months to exclude any effect is just innate immunity or immediate post vax neutralization titers of short duration.

[15] WER 2020, 28, 95, 325-336

Efficacy

The primary efficacy endpoint point estimate should be at least 50%, and the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate is >30%. As it is not possible to know the duration of protection of the vaccine after release of initial data, follow up of subjects must continue in order to estimate these.

Subgroup analyses of efficacy endpoints stratified by prior infection status at trial enrolment.

Efficacy data including a median follow-up duration of at least three months after completion of administration of all doses in the schedule

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 (including at least a subset of participants in late phase efficacy trials).
- Unsolicited adverse events in all study participants for at least 21–28 days after each study vaccination.
- Serious and other medically attended adverse events in all study participants for at least 6 months after completion of all study vaccinations.
- Longer safety monitoring may be needed for certain vaccine platforms (e.g., those that include novel adjuvants).

Specifically,

Phase 1 and 2 trials: longer term follow up, including data on serious adverse events, adverse events of special interest, and cases of severe COVID-19 among study subjects.

Phase 3 studies: safety data from a minimum number of vaccinees (see TRS 1004) including a median follow-up duration of at least three months after completion of administration of all doses in the schedule.

Reports should include:

- adverse events; cases of severe COVID-19 disease among study subjects; and cases of COVID-19 occurring at least 14 days after the last dose is administered.
- subgroup analyses of safety and efficacy endpoints stratified by prior infection status at trial enrolment.
- Data on sufficient cases of severe COVID-19 among trial participants to support low risk for Enhanced Disease.

Follow up:

Blinded study follow-up, for COVID19 disease and for SAEs, should last for at least one year (and preferably longer). This will enable further analysis of duration of efficacy and potential for risk of vaccine-induced COVID-19 disease enhancement in the presence of waning immunity. In the event that there is evidence of waning efficacy of a successful vaccine over the period of observation, participants in this trial may be randomized to prospectively designed controlled study of a booster dose.

Active safety follow-up must also be implemented in all vaccinees to further document safety: Local and systemic solicited adverse reactions collected for the defined duration of follow-up in an adequate number of subjects to characterize reactogenicity in each protocol-defined age cohort participating in the trial;

Manufacturers should provide safety data that as indicated in the list of adverse events of special interest proposed by WHO GACVS (WER 2020, 28, 95, 325-336)

Benefit Risk assessment Report

A detailed review of available data and objective Benefit and Risk assessment of the vaccine should be provided at the time of submission

Risk Management Plan (RMP)

A detailed RMP including pharmacovigilance plan should be provided

3.2. MANUFACTURING, QUALITY CONTROL AND LABELLING

The submission for EUL/PQ of vaccines should follow the ICH CTD format. In the CTD dossier, should indicate in the sections for which no information is available at the time of the initial submission “data or information not available”, “study ongoing” or “not applicable” as the case may be.

3.2.1. Characterization of cell banks

Full characterization of cell banks according to WHO Technical Report Series (TRS) 978, and any subsequent updates.

3.2.2. Characterization of master and working seed organism(s)

Full characterization of master and working seed organism(s), based on reference to the most appropriate WHO TRS.

3.2.3. Process validation

Process validation (based on quality risk assessment for the development stage) and demonstration of consistency of production at the production scale used for the lots to be distributed.

If deemed appropriate by WHO, data on clinical batches with a commitment to complete validation on production batches and to submit the data as part of lot release review may be considered.

N.B., if full characterization is not possible at the time of submission, adequate justification must be submitted as to why not, and a plan must be presented to address the data gaps
Validation of potency tests and other critical assays: If novel test methods have been developed, full description of the test development and qualification must be presented.

3.2.4. Justified specifications

Justified specifications for starting material, intermediates, and final products.

3.2.5. Stability data

Stability data for the vaccine produced at the scale produced for the lots must be supplied. If available, accelerated stability data must be included. For vaccines being assessed for emergency use, WHO will consider programmatic suitability and may consider candidate vaccines with characteristics that would not be accepted for prequalification.

a) Vaccines requiring storage at less than -20°C are generally not accepted for prequalification. However, under this emergency procedure, such vaccines can be considered. Upon receipt of such an application, WHO staff responsible for emergency response vaccine deployment will be informed by the WHO EUL Secretariat, and will be requested to evaluate and consider whether recipient countries will require assistance with regards to infrastructure for vaccine storage and distribution at required temperatures.

b) Routinely, if a vaccine presented for prequalification requires storage below +2°C during its shelf-life period, a minimum period of storage between +2°C and +8°C of 6 months is required. Under this emergency procedure, vaccines with a shelf life at +2 to +8°C of less than 6 months may be considered. The application should include stability data at +2 to +8°C to determine the minimum acceptable storage period at +2 to +8°C. Upon receipt of such an application, WHO staff responsible for emergency response vaccine deployment will be informed by the WHO EUL Secretariat, and will be requested to evaluate and consider whether recipient countries will require assistance with regards to infrastructure for vaccine storage and distribution at required temperatures. Routinely, multi-dose vaccines for prequalification should contain adequate preservative, unless they are live-attenuated vaccines (where the preservative may have an adverse effect on the viability of the microbe). However, if a multi-dose vaccine submitted under this emergency procedure does not contain a preservative, information/plans on how such a vaccine could be safely managed in the field should be submitted.

3.2.6. Inspection reports

Inspection report(s) from the responsible NRA showing compliance with GMP requirements.

3.2.7. Process changes

If changes in the manufacturing process are introduce before the assessment is finalized or after the listing, these must be reported to WHO.

3.2.8. Labelling

1. Summary of product characteristic (information for healthcare provider)
2. Patient information leaflet
3. Container labelling
4. Any other instructional materials provided to the user.
5. A plan to help assure that prospective recipients and healthcare providers are adequately informed about the uncertainties regarding both the potential benefits and risks.