



CONSIDERATIONS FOR EVALUATION OF COVID19 VACCINES

Points to consider for manufacturers of COVID19 vaccines

Version 25 November 2020

Vaccine and Immunization Devices Assessment Team (VAX)
Prequalification Unit (PQT)
Regulation and Prequalification Department (RPQ)
Access to Medicine and Health Products (MHP)
World Health Organization, Geneva, Switzerland

Table of Contents

1. EXECUTIVE SUMMARY	4
2. INTRODUCTION.....	5
3. SUBMISSION AND REVIEW PROCESS	7
3.1. GENERAL	7
3.1.1. Format and content of an application.....	7
3.1.2. Screening of applications	7
3.2. ADDITIONAL NON-CLINICAL INFORMATION.....	8
3.3. CLINICAL ASSESSMENT.....	9
3.3.1. Clinical development programme	9
3.3.2. Requirement for the protocols of clinical trials that support application	9
3.3.3. Evidence of Ethics Committee approval of clinical trials	9
3.3.4. Evidence for Good Clinical Practices (GCP) conduct of each trial	9
3.3.5. Evidence for registration of each clinical trial	9
3.3.6. Clinical trial design	9
3.3.7. Statistical Considerations	10
3.3.8. Clinical trial end-point assays - relevance, validation and accreditation.....	11
3.3.9. Vaccine lots used in clinical studies and lot-to-lot consistency studies	11
3.3.10. Subject exposure to a new vaccine in clinical trials.....	12
3.3.11. Follow-up in clinical trials	12
3.3.12. Requirement for a risk management plan, or equivalent document as part of the CTD ..	12
3.3.13. Specific data should be submitted to answer the following questions	13
3.3.14. Minimum clinical criteria for EUL assessment.....	17
3.4. MANUFACTURING AND QUALITY CONTROL.....	19
3.4.1. Drug Substance.....	19
3.4.1.1. Manufacturer(s)	19
3.4.1.2. Description of Manufacturing Process and Process Controls	20
3.4.1.3. Cell banking system, characterization and testing.....	20
3.4.1.4. Characterization of Master and Working seed	21
3.4.1.5. Controls of Critical Steps and Intermediates.....	21
3.4.1.6. Process Validation and/or Evaluation	21
3.4.1.7. Analytical method validation	22
3.4.1.8. Manufacturing Process Development.....	22
3.4.1.9. Control of Drug Substance	22
3.4.1.10. Reference standards or materials.....	23
3.4.1.11. Container Closure System.....	23
3.4.1.12. Stability	23
3.4.2. Drug product.....	23

3.4.2.1.	Manufacture.....	23
3.4.2.2.	Pharmaceutical Development.....	23
3.4.2.3.	Components of the Drug Product	24
3.4.2.4.	Formulation Development.....	24
3.4.2.5.	Manufacturing Process Development.....	24
3.4.2.6.	Container Closure System.....	24
3.4.2.7.	Compatibility of diluents.....	25
3.4.2.8.	Batch Formula	25
3.4.2.9.	Description of Manufacturing Process and Process Controls	25
3.4.2.10.	Controls of Critical Steps and Intermediates.....	25
3.4.2.11.	Process Validation and/or Evaluation	26
3.4.2.12.	Control of Drug Product.....	26
3.4.2.13.	Control of excipients, stabilizers, adjuvants.....	26
3.4.2.14.	Reference Standards or Materials.....	27
3.4.2.15.	Stability	27
3.4.2.16.	Post-approval Stability Protocol and Stability Commitment	28
3.4.3.	Changes	28
3.4.4.	Inspection reports	29
3.4.5.	Labelling.....	29

1. EXECUTIVE SUMMARY

This document provides advice to manufacturers on both the process and 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 National Regulatory Authorities (NRAs)¹ of record² will guide WHO's decision on which pathway (PQ or EUL) to follow for each vaccine.

The document should not be read as a standalone document.; other relevant documents, as cited, must also be consulted.

Only vaccines that have undergone phase IIb or phase III studies and have been submitted to the NRA of record should be submitted for consideration. WHO may review rolling submission, however, a decision on listing will not be made until the NRA of record has approved/authorized the vaccine.

As the data, at the moment of submission, will not be complete (i.e. clinical trials will be ongoing) this document outlines what information needs to be provided in the dossier (rolling submissions and complete dossier) for WHO to review and formulate a decision on listing.

The dossier should follow the format of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Common Technical Document³ (ICH CTD) as indicated in the EUL and PQ procedures. This means that Modules 2 to 5 should include the same items, although not all of the information may be available at the time of submission. In the CTD dossier, the applicant 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. Adequate justification must be provided for any unavailable data, and a plan must be presented to address the data gaps, when applicable.

This document provides a guidance on the level of expected completeness of information, taking into consideration that the development is still ongoing and the criteria that will be used to assess clinical trial design, endpoints, statistical criteria, as well as manufacturing, quality control and non-clinical data to address the potential for vaccine-associated enhanced disease. Post-authorization commitments will be part of the listing conditions, depending on existing information and a benefit-risk assessment.

¹ See Technical Report Series 1003 and 1010 for definition of types of NRAs

² NRA of record is the NRA that first approved the vaccine and is responsible for the oversight of such vaccine

³ <https://www.ich.org/page/ctd>

WHO has published a call for Expression of Interest for those manufacturers with vaccine candidates in advanced stages of development (Phase IIb/III) that expect to have the vaccine approved by their NRA of record within the next six months. Those products that meet the criteria set in this document will be considered for submission after a pre-submission meeting to discuss specific issues related to available data, estimated timelines for submission of new data, submissions to NRA of record and timelines for their approval/authorization.

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)⁴ 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 data⁵. Both procedures include, for each product, the evaluation of data submitted contained in the CTD format.

The EUL is not equivalent or an alternative to WHO prequalification, and should not be thought of as such. The EUL is a special procedure for unlicensed vaccines, medicines and in vitro diagnostics in the event of a Public Health Emergency (PHE) when the community/public health authorities may be willing to tolerate less certainty about the efficacy and safety of products, given the morbidity and/or mortality of the disease and the lack or paucity of treatment, diagnosis/detection or prevention options. The procedure intends to provide a time-limited listing for unlicensed products in an emergency context when limited data are available and the products are not yet ready for application for prequalification⁶. As part of the EUL, the manufacturer is expected to complete the development of the product and submit for licensure and WHO prequalification.

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 the reviews, WHO focuses on information that may

⁴ <https://www.who.int/teams/regulation-prequalification/eul/eul-vaccines>

⁵ https://www.who.int/immunization_standards/vaccine_quality/EUL/en/

⁶ https://www.who.int/immunization_standards/vaccine_quality/pq_revision2010/en/

not be part of the NRA approval process, although in practice they also do at least a verification of what is expected to have been evaluated by the NRA. Any vaccine submitted for WHO assessment through the EUL or PQ procedure should have been submitted to the NRA of record (for emergency use approval or equivalent or standard licensure/marketing authorization). However, manufacturers may submit data packages (rolling submissions for non-clinical, CMC, clinical) to WHO when they submit to their NRA of record to advance the review.

The general principles described in the WHO Guidelines below apply to all Covid-19 vaccines and should be followed:

1. “Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies”, WHO Technical Report Series 978, Annex 6, 2013 ⁷
2. WHO EUL document ⁸
3. “Guidelines on clinical evaluation of vaccines: regulatory expectations”, WHO Technical Report Series 1004, Annex 9, 2017 ⁹
4. COVAX SAGE Compendium of Covid-19 vaccine research questions ¹⁰
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, 24–28 August 2020. ¹¹
6. “Points to Consider for assuring the quality, safety and efficacy of RNA vaccines”¹² (currently under development)¹³
7. WHO guidelines on nonclinical evaluation of vaccines. TRS 927, Annex 1 ¹⁴
8. Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines. TRS 987, Annex 2 ¹⁵

⁷ http://www.who.int/immunization_standards/vaccine_quality/TRS_978_61st_report_Annex_6_PQ_vaccine_procedure.pdf?ua=1

⁸ <https://www.who.int/medicines/publications/EULprocedure.pdf?ua=1>

⁹ http://www.who.int/biologicals/expert_committee/WHO_TRS_1004_web_Annex_9.pdf

¹⁰ https://www.who.int/docs/default-source/immunization/sage/2020/october/sage-wg-critical-questions-covid19-vaccine.pdf?Status=Temp&sfvrsn=6a98fce2_6&ua=1

¹¹ <https://www.who.int/publications/m/item/DNA-post-ECBS-1-sept-2020>

¹² Currently under development and to be published at <https://www.who.int/biologicals>

¹³ https://www.who.int/publications/m/item/WHO-ECBS-aug-2020-executive_summary

¹⁴ https://www.who.int/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/ANNEX%201Nonclinical.P31-63.pdf?ua=1

¹⁵ https://www.who.int/biologicals/areas/vaccines/TRS_987_Annex2.pdf?ua=1

9. Recommendations for the Evaluation of Animal Cell Cultures as Substrates for the Manufacture of Biological Medicinal Products and for the Characterization of Cell banks. TRS 978, Annex 3¹⁶
10. WHO good manufacturing practices for biological products. TRS 999, Annex 2¹⁷

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.

The decision for listing will be based on a risk-benefit assessment, of existing evidence of quality, safety and efficacy and will include a set of post-listing commitments.

3. SUBMISSION AND REVIEW PROCESS

3.1. GENERAL

3.1.1. Format and content of an application

The format of the application should follow the ICH CTD format. Refer to “Vaccine Prequalification Dossier”¹⁸

3.1.2. Screening of applications

The CTD of a vaccine submitted for evaluation is expected to have adequate information to support the quality, efficacy, immunogenicity and safety of that product, and evidence that such information is supportive for a wide use of the vaccine if listed through the EUL or PQ procedures.

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

¹⁶ https://www.who.int/biologicals/vaccines/TRS_978_Annex_3.pdf

¹⁷ https://www.who.int/biologicals/expert_committee/WHO_TRS_999_FINAL.pdf?ua=1

¹⁸ http://www.who.int/immunization_standards/vaccine_quality/VaccinePQ-dossier_Dec2017.pdf?ua=1

3.2. 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, as recommended in the WHO guidelines on the nonclinical evaluation of vaccine adjuvants, must be submitted.¹⁹

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-enhanced disease (VED). Current knowledge and understanding of the potential risk of COVID-19 vaccine-enhanced disease (VED) 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 or and non-human primates) are considered important to address the potential for vaccine-enhanced disease (VED). Bio/Immunological markers to be evaluated should include relative levels of neutralizing vs non-neutralizing antibodies, antibody affinity, T-cell response profile (Th1/Th2), characterization of lung histopathology,²⁰ and other potential complications.

Studies should include an evaluation of humoral, cellular, and functional immune responses, as appropriate to each of the included COVID-19 antigens, with consideration of the adjuvant effect. 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. The functional activity of immune responses should be evaluated in vitro in neutralization assays using either wild-type virus or pseudovirus microneutralization. Assays for vaccines with multiple components or adjuvants should be measured with either a multiplex assay or separate single assays. The assays used for immunogenicity evaluation should be validated for their intended purpose and calibrated against WHO international standards where available.

Detailed WHO guidelines on the design, conduct, analysis and evaluation of nonclinical studies of vaccines are available in WHO TRS 927.

¹⁹ https://www.who.int/biologicals/areas/vaccines/ADJUVANTS_Post_ECBS_edited_clean_Guidelines_NCE_Adjuvant_Final_17122013_WEB.pdf

²⁰ Vaccine 2020, Lambert et al. doi: 10.1016/j.vaccine.2020.05.064

3.3. CLINICAL ASSESSMENT

3.3.1. Clinical development programme

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

3.3.2. 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.

3.3.3. 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.

3.3.4. 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 independent monitoring of the trial conduct, audits by the sponsor, available NRA inspection reports or Data and Safety Monitoring Board (DSMB) reports. Manufacturers should consult WHO Guidelines for good clinical practice (GCP) for trials on pharmaceutical products should be consulted (TRS 850 Annex 3).

3.3.5. 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.

3.3.6. Clinical trial design^{21 22}

Phase IIB/III efficacy trials should be randomized, blinded, and placebo controlled or active-controlled (when a safe and effective COVID-19 vaccine is available). An individually randomized controlled trial with 1:1 or 2:1 randomization between vaccine and placebo groups is usually the most efficient study design for demonstrating vaccine efficacy.

²¹ FDA Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry June 2020.

²² Guidelines on clinical evaluation of vaccines: regulatory expectations”, WHO Technical Report Series 1004, Annex 9, 2017

Other types of randomization, such as cluster randomization, may be acceptable if there is evidence that potential biases have been avoided.

Protocols for late stage (phase IIb/III) trials (including adaptive trials) should include pre-specified criteria for critical decisions. Protocols for early stage trials (phase I/IIa) should be designed to characterize optimal vaccine formulations, doses, and regimens efficiently and safely. Frequent interactions with NRAs may be needed to guide decision making in adaptive or seamless trials in their early stages.

Follow-up of study participants for COVID-19 outcomes (especially severe COVID-19 manifestations) should continue as long as feasible, and ideally at least one to two years. This is to allow for an adequate assessment on the duration of protection and potential for vaccine-associated Enhanced Disease (VAED) 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 NRA may be necessary to address ethical issue of breaking the blind and offering vaccine to placebo recipients.

A Data and Safety Monitoring Board should be established to provide periodic independent review of safety data at appropriate intervals, as well as to conduct a review of any interim efficacy data

3.3.7. Statistical Considerations^{23 24 25}

The primary efficacy endpoint in COVID-19 vaccine trials should be a clinically driven endpoint (e.g. laboratory confirmed first episode of COVID-19). If an immune correlate of protection becomes established, it could be used as the primary efficacy endpoint.

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

A statistical success criterion for an interim analysis for early detection of efficacy should be at least as rigorous as the end of study success criterion.

²³ FDA Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry June 2020

²⁴ WHO Target Product Profiles (TPP) for COVID-19 Vaccines (Version 3 - 29 April 2020)

²⁵ Guidelines on clinical evaluation of vaccines: regulatory expectations", WHO Technical Report Series 1004, Annex 9, 2017

A lower bound $\leq 30\%$ 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 based of efficacy 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 enhanced disease, or other adverse reactions 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 for the populations and locales in which the trial will be conducted.

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

Any serological correlate of protection used in the analyses must be justified and supported with best scientific evidence available. Assays should consider the assessment of a functional antibody response along with immunoglobulin serum titre unless the immunoglobulin measured is clearly demonstrated as an immune correlate of protection. As immune responses can vary between gender, age groups or with other target groups, the clinical trial endpoints should as much as possible include adequate assessment of these populations. 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. The assays should be validated and run in a central laboratory, if possible.

3.3.9. 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 consecutive lots with the same formulation intended for marketing are used in the late stages of the clinical development

programme. If clinical lot to lot consistency data has not been demonstrated, CMC consistency data must be provided.

3.3.10. 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. When considering the pre-licensure safety database the need for a sufficient sample size to estimate adverse events (AE) rates with precision is an important factor. For example, a total database of 3000 subjects across all trials and populations provides a 95% chance of observing one instance of an AE that occurs on average in 1 in 1000 subjects. (The number that would provide a 95% chance of observing one instance of an AE that occurs on average in 1 in 10 000 subjects is 30 000). 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. Trials may not be powered to demonstrate vaccine efficacy by subgroup, e.g., age. The safety database 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.

3.3.11. 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 enhanced disease as immune responses to the vaccine wane. This follow up should be active and not reliant on spontaneous reports. A follow-up of at least one year may be expected for efficacy and immunogenicity assessment, depending on the clinical endpoint requirements.

3.3.12. Requirement for a risk management plan, or equivalent document as part of the CTD

Risk management plans (RMP), 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.

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

Sponsors should consider whether, and how, their submission to PQ addresses the following questions. These are posed with the intention of aiding the sponsor during their vaccine development program and assembly of their submission and do not necessarily represent the only questions that PQ would consider during their assessment. The questions may not apply to all vaccine types. Only vaccines that have undergone phase IIb or phase III studies and have received authorization from a functional NRA (or have been submitted for evaluation) should be submitted for consideration. Rolling review of submissions may be acceptable.

Clinical efficacy

- i. What is the evidence of an effect of vaccination on efficacy against COVID-19 (regardless of severity); mild symptomatic, moderate, and severe disease; hospitalizations and death. How does efficacy vary by age-group (children, younger adults, older adults), by sex, in pregnant and lactating women, and in specific co-morbidity risk groups?
 - Measured as % vaccine efficacy and 95% confidence intervals
- ii. What is the evidence of an effect of vaccination on efficacy against SARS-CoV-2 infection?
 - Measured as percentage vaccine efficacy and 95% confidence intervals
 - Measured difference in viral load (PCR Ct values) in upper respiratory tract samples
 - Measured as seroconversion to viral antigens not contained in the vaccine
- iii. What is the evidence of the efficacy of post-infection immunization?

The WHO Target Product Profile should serve as a guide.²⁶

Immunogenicity

- i) What is the evidence of induction and levels of neutralizing antibodies and of immunoassay-measured antibodies after partial or full primary vaccination in the different groups listed above (under clinical efficacy)?
 - Measured as concentrations/titres of antibodies or seroconversion rates versus pre-vaccination values or, if a correlate is established, seroprotection rates.

²⁶ WHO Target Product Profile (TPP) for COVID-19 Vaccine (version-3 29 April 2020)

- ii) What is the evidence that immunobridging can be used to estimate vaccine efficacy in specific groups for which clinical efficacy is not available from clinical trials? This is important as, based on the inclusion/exclusion criteria of the currently ongoing large phase III trials, certain population and age groups have in some instances been excluded from participation (e.g. infants, those with co-morbidities, pregnant and lactating women, etc.).
- iii) What is the evidence of persistence of protective / neutralizing / immunoassay-measured antibodies over time (over an interval lasting as long as feasible after completion of partial or full primary vaccination in the different groups listed above?)
- iv) For vaccines with regimens of two or more doses, what is the evidence for interchangeability of vaccines?

Effectiveness

- i) What is the evidence from observational post-implementation studies on vaccine effectiveness (in different populations)?
- ii) What is the evidence of effectiveness of the intervention in specific subpopulations?
- iii) What is the evidence of vaccine effectiveness after a single dose of vaccination or after using an incomplete schedule?

Duration of protection

What is the evidence of continued efficacy/ effectiveness of vaccination (in different populations) after completion of 1 or 2 dose course of immunization in the different at-risk populations (e.g. elderly)? This can be measured as decay in antibody titers over time.

Questions on indirect effects and biomarkers

Transmission

- i) What is the evidence of the relation of viral shedding post-vaccination and SARS-CoV-2 transmissibility?
 - Measured as viral load among those infected
 - Other measures of infectiousness (e.g., subgenomic viral RNA)

- ii) What is the evidence of an effect of immunization on the duration of shedding of SARS-CoV-2?
 - Measured as viral shedding through active surveillance of respiratory tract sampling in vaccinated and control individuals

- iii) What is the evidence of reduction in new SARS-CoV-2 infections in contacts of vaccinated as compared to unvaccinated study subjects who become infected?

(For example: this could be answered by adjunctive protocols to large randomized controlled trials (RCTs), comparing infection rates among contacts of vaccinated and control study subjects)

- iv) What is the evidence of reduced rates of infection in unvaccinated individuals in vaccinated populations?

(For example: this could be answered by cluster randomized studies focusing on infection rates in un-vaccinated members of vaccinated clusters – if logistical and ethical challenges of undertaking such trials could be overcome)

Biomarkers and correlates of protection

- i) What is the evidence from functional antibody assays /neutralizing antibody assays? What is the evidence of their standardization and use in phase 1-3 clinical trials? What is the evidence that one or more of the described assays have been correlated to clinical protection?
- ii) What is the evidence from immunoassays used to assess responses to vaccines? What is the evidence that these assays have been correlated to functional/neutralization assays or to clinical protection?
- iii) What is the evidence concerning characterization of T cell responses, both to naturally acquired infection and to vaccination that are (expected to be) protective?
- iv) What is the evidence that certain aspects of immune responses to vaccination (e.g. predominant development of certain types of CD4+ T cells, such as T helper cells (Th) type 1, over Th type 2 or Th type 17 and their distinct cytokine production patterns, elicited by the specific vaccine) are predictive of effective protection and/or absence of vaccine enhanced disease when exposed to SARS-CoV-2 following immunization?

Target populations

- i) How to extrapolate to potential target populations (age, ethnicities, co-morbidities) for whom there may be insufficient data (effectiveness, safety). It is acknowledged that data for all target groups may not be available when vaccines is considered for EUL/PQ in the early stages of the response to COVID-19.

Vaccine safety

- i) What is the evidence on rates of local and systemic reactogenicity signs and symptoms (e.g., pain at injection site, fever, headaches, malaise, etc.) using standardized definitions and ascertainment methods in the different target-populations and what is the impact on tolerability of the vaccine?
- ii) What is the evidence of disease enhancement in either vaccine recipients subsequently exposed to the virus, in vaccine recipients with prior infection/pre-existing antibodies or those with incomplete immunization schedule?
- iii) What is the evidence of any suspected unexpected serious adverse reactions (SUSARs), including but not limited 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 - PIMS-TS)?
- iv) What is the evidence of adverse events of special interest (AESI), related or possibly related serious adverse events (SAE) and medically attended adverse events (MAAE) after vaccination (in all vaccinees with a minimum of 3 months, preferably up to 12 months, of follow-up after completion of administration of all doses in the vaccination schedule; in line with regulatory requirements and the points to consider for manufacturers of COVID-19 vaccines)?
- v) What is the evidence of adverse maternal and neonatal outcomes after vaccination of pregnant women?
- vi) What is the evidence on co-administration of COVID-19 vaccines with other vaccines included in routine immunization schedule leading to decreased immune response to either vaccine?
- vii) What is the evidence that vaccinated persons are less likely to adopt other measures to reduce the risk of infection?

Manufacturers should provide safety data as indicated in the list of adverse events of special interest proposed by WHO GACVS.²⁷ The Brighton Collaboration standardized case definitions, whenever available, should be applied to assess level of diagnostic certainty.

Benefit Risk Assessment Report.

A detailed review of available data and objective Benefit and Risk assessment of the vaccine [e.g., via the appropriate Brighton Collaboration standardized templates for benefit–risk assessment of vaccines (by technology platforms)] should be provided at the time of submission.

3.3.14. 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 after vaccination for a one dose regimen or at least one week after the last vaccination of a multidose regimen. Cases should be accumulated for at least 2 months to exclude that any effect is just only innate immunity or immediate post vaccination neutralization titers of short duration.

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%. In order to evaluate the duration of protection by the vaccine, subjects should continue to be followed for a period to estimate this.

²⁷ WER 2020, 28, 95, 325-336

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

Efficacy data including a median follow-up duration of at least two 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 28 days after each study vaccination.
- Serious 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: data on short and 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 two 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 COVID-19 among trial participants to investigate the low risk for Vaccine Associated Enhanced Disease (VAED).

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. Vaccinated subjects experiencing a respiratory infection in the follow up period should be tested for specific pathogen.

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 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 [e.g., via the appropriate Brighton Collaboration standardized templates for benefit–risk assessment of vaccines (by technology platforms)] should be provided at the time of submission.

Risk Management Plan

A detailed RMP including pharmacovigilance and risk minimization plans (or equivalent documents) should be provided.

3.4. MANUFACTURING AND QUALITY CONTROL

The following list indicates the key information in Module 3 of the CTD that should be complete in the submissions to consider the dossier for review.

3.4.1. Drug Substance**3.4.1.1. Manufacturer(s)**

This should be the manufacturer and manufacturing sites that will be intended for EUL/PQ, which may not be the same as those included in the submission to the NRA of record for the Conditional Marketing Authorization, Emergency Use Approval or equivalent.

3.4.1.2. Description of Manufacturing Process and Process Controls

A flow diagram that illustrates the manufacturing route from starting materials (Master and Working Cell Banks, Master and Working Seeds, starting materials of biological origin) to the Drug substance should be provided.

Relevant information for each stage of the upstream and downstream processes, should be included. Critical steps and critical intermediates for which specifications are established should be identified.

A description of each process step in the flow diagram should be provided, including major equipment and process controls, including in-process tests and operational parameters, with acceptance criteria.

Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided.

If applicable, reprocessing procedures with criteria for reprocessing of any intermediate or the drug substance should be described.

A description of the filling procedure for the drug substance, process controls (including in process tests and operational parameters), and acceptance criteria should be provided.

3.4.1.3. Cell banking system, characterization and testing

Full characterization of the cell banks according to relevant WHO guidelines should be provided and should include viral safety studies.

Information on the cell banking system, should include quality control activities, and cell line stability during production and storage (including procedures used to generate the Master and Working Cell Bank(s)).

If applicable to the manufacturing platform, information on the source of the cell substrate and analysis of the expression construct used to genetically modify cells and incorporated in the initial cell clone used to develop the Master Cell Bank should be provided.

3.4.1.4. Characterization of Master and Working seed

Full characterization of Master and Working Seed, complete history of the virus used to prepare the Virus Seed

For viral-vectored vaccines, the use of any viral vector should be based on a master and working seed lot system, analogous to the cell banking system used for production cells. The origin of all genetic components of the vaccine and their function should be specified to allow for a clear overall understanding of the functionality of the vaccine and of how it is attenuated or made replication incompetent by genetic engineering.

3.4.1.5. Controls of Critical Steps and Intermediates

Tests and acceptance criteria for all critical steps (with justification including experimental data) should be provided for all critical steps of the manufacturing process to ensure that the process is controlled.

Information on the quality and control of intermediates isolated during the process should be provided.

3.4.1.6. Process Validation and/or Evaluation

Process validation (based on quality risk-based approach) and demonstration of consistency of production at the production scale used for the lots to be distributed should be provided.

Sufficient information should be provided on validation and evaluation studies to demonstrate that the manufacturing process is suitable for its intended purpose and to substantiate selection of critical process controls (operational parameters and in-process tests) and their limits for critical manufacturing steps (e.g., cell culture, harvesting, purification, and modification).

Use of multiple sites for production of Drug Substance should be supported by demonstration of analytical comparability.

As an alternative to the traditional process validation, continuous process verification can be utilised in process validation protocols for the initial commercial production and also for manufacturing process changes for the continual improvement throughout the remainder of the product lifecycle.

3.4.1.7. Analytical method validation

If novel test methods have been developed for potency tests and other critical assays, full description of the test development and qualification must be provided.

The analytical procedures and corresponding validation should be cross-referenced or provided as part of justifying the selection of critical process controls and acceptance criteria.

For manufacturing steps intended to remove or inactivate viral contaminants, the information from evaluation studies should be provided in detail.

3.4.1.8. Manufacturing Process Development

A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing nonclinical, clinical, scale-up, pilot, and, if available, production scale batches.

The developmental history of the manufacturing process, should be provided. The description of change(s) made to the manufacture of drug substance batches used in support of the submission (e.g., nonclinical or clinical studies) should include, for example, changes to the process or to critical equipment. The reason for the change should be explained. Relevant information on drug substance batches manufactured during development, such as the batch number, manufacturing scale, and use (e.g., stability, nonclinical, reference material) in relation to the change, should be provided. The significance of the change should be assessed by evaluating its potential to impact the quality of the drug substance (and/or intermediate, if appropriate).

A discussion of the data, including a justification for selection of the tests and assessment of results, should be included. Testing used to assess the impact of manufacturing changes on the drug substance(s) and the corresponding drug product(s) can also include nonclinical and clinical studies. Cross-reference to the location of these studies in other modules of the submission should be included.

3.4.1.9. Control of Drug Substance

The specification for the drug substance should be provided and justified.

Analytical procedures for testing of the drug substance should be validated.

Description of batches and results of batch analyses should be provided to demonstrate lot consistency.

3.4.1.10. Reference standards or materials

Information on Reference standards or reference materials should be provided.

3.4.1.11. Container Closure System

A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate).

3.4.1.12. Stability

This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, retest date or shelf-life, where relevant. The post-approval stability protocol should be included.

3.4.2. Drug product

3.4.2.1. Manufacture

Manufacturer(s) of Drug Product, Filler/packagers must be indicated for the vaccine that will be submitted for EUL/PQ, which may be different from the one submitted to the NRA of record for Conditional Marketing Authorization, Emergency Use Approval or equivalent.

If the manufacturer of the Drug Substance is different from the manufacturer of the Drug Product it should be indicated.

Facilities and Equipment included in the dossier should be for those sites where the product intended for supply through COVAX facility is manufactured.

3.4.2.2. Pharmaceutical Development

The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should

identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and drug product quality. Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical Development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the application.

3.4.2.3. Components of the Drug Product

Drug Substance

The compatibility of the drug substance with excipients/ stabilizers/adjuvants listed should be discussed.

If the manufacturer of the Drug Substance is different from the manufacturer of the Drug Product it should be indicated.

Excipients, stabilizers, adjuvants

The choice of excipients/stabilizers/adjuvants listed, their concentration, their characteristics that can influence the drug product performance should be discussed relative to their respective functions.

3.4.2.4. Formulation Development

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation in the finished product should be discussed. Results from comparative in vitro studies or comparative in vivo studies should be discussed when appropriate.

3.4.2.5. Manufacturing Process Development

The selection and optimisation of the manufacturing process, in particular its critical aspects, should be explained. Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in finished product that can influence the performance of the product should be discussed.

3.4.2.6. Container Closure System

The suitability of the container closure system used for the storage, transportation (shipping) and use of the drug product should be discussed. This discussion should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when

presented as part of the drug product).

A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included where appropriate. For non-functional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

3.4.2.7. Compatibility of diluents

If the vaccine is lyophilized, the compatibility of the drug product with reconstitution diluent(s) or dosage devices – if applicable- should be addressed to provide appropriate and supportive information for the labeling.

3.4.2.8. Batch Formula

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.

3.4.2.9. Description of Manufacturing Process and Process Controls

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified. A narrative description of the manufacturing process, including packaging, that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail.

Equipment should, at least, be identified by type and working capacity, where relevant. Steps in the process should have the appropriate process parameters identified.

3.4.2.10. Controls of Critical Steps and Intermediates

Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps of the manufacturing process, to ensure that the process is controlled. Information on the quality and control of intermediates isolated during the process should be provided.

3.4.2.11. Process Validation and/or Evaluation

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

Use of multiple sites for production of Drug Product should be supported by demonstration of analytical comparability.

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 analysis

3.4.2.12. Control of Drug Product

The specification(s) for the drug product and the analytical procedures used for testing the drug product should be provided.

Analytical validation information, including experimental data, for the analytical procedures used for testing the drug product, should be provided.

Justification for the proposed drug product specification(s) should be provided.

3.4.2.13. Control of excipients, stabilizers, adjuvants

The specifications for excipients and the analytical procedures used for testing the excipients should be provided, where appropriate.

Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate.

Justification for the proposed excipient specifications should be provided, where appropriate.

For excipient(s) and adjuvants used for the first time in a drug product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the drug substance format

3.4.2.14. Reference Standards or Materials

Information on the reference standards or reference materials used for testing of the drug product should be provided.

3.4.2.15. Stability

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life.

Stability data for the vaccine produced at the scale produced for the lots at the scale intended for distribution should be supplied.

Generally, real-time stability from three full-scale production lots is preferred. With appropriate justification and discussion with the WHO, a scientific risk-based approach to determine the proposed vaccine shelf life in the absence of real time stability data on the commercial batches may be considered. For example, data generated from smaller lots, such as clinical or engineering lots, and/or data generated on a different vaccine using a similar process and/or manufacturing platform, may be appropriate for submission in support of the initial recommended shelf-life for the vaccine.

Consideration of platform stability data, prior knowledge from early clinical batches or statistical modelling may also be applied to forecast expiry of product.

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included

Long term stability studies as part of post-listing commitments will be discussed.

WHO may consider candidate vaccines with characteristics that would not be accepted for prequalification (programmatic suitability criteria)²⁸.

- a) Vaccines requiring storage at less than -20°C are generally not accepted for prequalification. However, under this emergency procedure, such vaccines can be

²⁸ https://www.who.int/immunization_standards/vaccine_quality/ps_pg/en/

considered. Upon receipt of such an application, WHO staff responsible for emergency response vaccine deployment will be informed by the WHO EUL/PQ 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/PQ 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.
- c) 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 virus). 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.
- d) The requirement for VVM may be waived while data is generated. Accelerated stability data must be included. This information is required to assess if the stability profile at different temperatures matches any existing VVM category.

3.4.2.16. Post-approval Stability Protocol and Stability Commitment

The post-approval stability protocol and stability commitment should be provided. As data for real time stability will be limited at the time of submission, updated information will be part of the post listing commitments.

3.4.3. Changes

If changes in the manufacturing process are introduced before the assessment is finalized or after the listing, these must be reported to WHO and all information provided for evaluation before the final report is prepared. Post listing changes must be reported according to the Guidance on reporting variations to a prequalified vaccine.

3.4.4. Inspection reports

Inspection report(s) from the responsible NRA showing compliance with GMP requirements. Taking in consideration the current challenges due to the COVID-19 pandemic, the WHO PQT/INS is considering various measures of regulatory flexibility including waving an on-site inspection and as a temporary measure, carrying out a desk assessment to determine the compliance of the site with Good Manufacturing Practices (GMP) and Quality Management System (QMS) requirements.

In cases where an inspection was deemed not required, a valid GMP certificate for the facility should be provided.

3.4.5. Labelling

Vial label, carton label and package insert should follow the models provided by WHO.

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.