

Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2

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1. INTRODUCTION

- Infectious disease preventive vaccine is a medical product to activate the immune system against specific antigen. For general considerations regarding nonclinical and clinical evaluations of investigational preventive vaccines for infectious diseases, Guidelines for Nonclinical Studies of Preventive Vaccines for Infectious Diseases (PFSB/ELD Notification No. 0527-1, dated May 27, 2010)¹⁾ and Guidelines for Clinical Studies of Preventive Vaccines for Infectious Diseases (PFSB/ELD Notification No. 0527-5, dated May 27, 2010)²⁾ can be used for reference.
- As a result of the recent pandemic of SARS-CoV-2 infectious disease (COVID-19), more than 20 million people have been affected to date worldwide. Vaccines to prevent SARS-CoV-2 infectious disease (SARS-CoV-2 vaccines) are being developed using various modalities such as inactivated virus vaccine, recombinant protein vaccine, mRNA vaccine that uses lipid nanoparticles (LNPs) as a carrier (LNP-mRNA vaccine), DNA vaccine, and recombinant virus vaccine with a recombinant virus vector and so on.
- This document presents basic principles concerning the efficacy and safety evaluation to develop a SARS-CoV-2 vaccine in Japan, based on the situation as of August 2020. It should be noted, however, that although the principles presented in this document are based on our knowledge at present and have been developed after discussions with experts on infectious diseases and vaccines, they may change in accordance with new findings and the status of SARS-CoV-2 vaccine development in Japan and overseas. Also this document shows one of examples concerning the benefit/risk evaluation of SARS-CoV-2 investigational vaccines and at the time of the regulatory review approval for each investigational vaccine, its benefit/risk will be reviewed taking into account its characteristics.
- For principles concerning the quality of a SARS-CoV-2 vaccine, the ICH guidelines regarding the quality of drugs and biological medicines, and existing guidelines in Japan and overseas can be used,³⁾⁻¹⁰⁾ depending on the modality of the investigational SARS-CoV-2 vaccine. Investigational products used in clinical trial must be controlled in accordance with Good Manufacturing Practice for Investigational Drugs (GMP-ID).¹¹⁾

2. NONCLINICAL STUDY

- Development of SARS-CoV-2 vaccine candidates has been needed to rapidly move forward to clinical trials. Principles for SARS-CoV-2 vaccine candidates to support proceeding to a first-in-human clinical trials and Phase III trials are presented in the summary reports of the workshops organized by the International Coalition of Medicines Regulatory Authorities (ICMRA), Global Regulatory Workshops on COVID-19 Vaccine Development (March 18, 2020 and June 22, 2020).^{12), 13)}

2.1. Pharmacological study

- The following nonclinical pharmacology assessments are generally required to support clinical trials:
 - Assessment of immunogenicity
 - ✓ To confirm production of SARS-CoV-2 antigen-specific antibodies
 - ✓ To confirm production of neutralizing antibodies to SARS-CoV-2
 - ✓ To analyze characteristics of the immune response induced by SARS-CoV-2 (e.g., SARS-CoV-2 antigen-specific antibody titer, neutralizing antibody titer, characterization of IgG subclass, and cytokine production)
 - ✓ To confirm induction of cell-mediated immunity to SARS-CoV-2
 - Assessment of anti-infective/disease-preventive effect
 - ✓ The anti-infective/disease-preventive effect against SARS-CoV-2 should be assessed in an animal model(s) of the infection.
 - ✓ The correlation with immune responses such as the SARS-CoV-2 antigen-specific antibody titer, the neutralizing antibody titer, and cell-mediated immunity should be assessed in an animal model(s) of infection

Each assessment should be validated to ensure appropriate assessment.

- Any SARS-CoV-2 vaccine candidate should be required to confirm function as an infectious disease preventive vaccines and to assess immunogenicity of the vaccine candidate before starting clinical trials since nonclinical safety assessment to support human safety should be conducted in relevant animals, which show immune response against the vaccine candidate. In addition, in order to estimate the potential risk of disease enhancement that can be elicited by administration of the SARS-CoV-2 vaccine (see Section 2.4), the immune response induced by administration of the vaccine candidate must also be characterized prior to the initiation of the clinical trials.
- The assessments of anti-infective/disease-preventive effect of infectious disease in animal model(s) should be conducted as early as possible, although they can be done in parallel with early phase of clinical trials.

2.2. Nonclinical Safety study

- For the nonclinical safety studies to support the clinical trials, Guidelines for Nonclinical Studies of Preventive Vaccines for Infectious Diseases and the summary reports of ICMRA Workshops on COVID-19 Vaccine Development can be useful as reference.
- To develop the SARS-CoV-2 vaccine, the nonclinical safety should be assessed. Conducting nonclinical safety studies of the SARS-CoV-2 vaccine candidate in parallel with the clinical trials can be accepted if the SARS-CoV-2 investigational vaccine is a LNP-mRNA vaccine, DNA vaccine, or recombinant virus vaccine, and the nonclinical safety can be explained by using the results of nonclinical safety studies and clinical studies of other LNP, DNA plasmid vector, or recombinant vector virus.
- Nonclinical safety of a SARS-CoV-2 vaccine candidates should be conducted according to Good Laboratory Practice (GLP) regulation.¹⁴⁾ To support clinical trials, assessment of safety pharmacology, general toxicity (multiple dose toxicity), and topical irritation are usually required.

- The test substance used for nonclinical safety studies should be a formulation that properly reflects the characteristics (composition, formulation, manufacturing process and control, etc.) of the product used for clinical trials.
- The dose in preclinical safety studies should be the maximum human dose in the clinical trials. If it is not feasible, administering at multiple sites should be considered, taking into account animal welfare (3Rs principles).¹⁵⁾
- In nonclinical safety studies, it is preferable to use animal species susceptible to the SARS-CoV-2 vaccine candidate. At least one animal species in which the vaccine candidate can induce immune response should be used.
- Stand-alone nonclinical studies to assess safety pharmacology and local tolerance are not recommended if they can be assessed in repeated-dose toxicity studies.
- Repeated-dose toxicity should be assessed considering the followings:
 - ✓ Number of doses should be equal or exceed the number of doses proposed in humans.
 - ✓ Systemic toxicity can be assessed even if the route of administration is different from that intended for use in the clinical trials as long as an adequate immune response is induced, while local tolerance should be assessed by the intended therapeutic route .
- Reproductive and developmental toxicity should be assessed considering the followings:
 - ✓ Fertility can be assessed as part of repeated-dose toxicity studies by through standard histopathological examination on reproductive organs.
 - ✓ Given that women of childbearing potential can be a recipient of the SARS-CoV-2 vaccine, assessment of embryo-fetal development, pre-postnatal development including maternal function should be conducted.
 - ✓ Generally, reproductive and developmental toxicity studies can be conducted by the time of marketing application. If, however, there is any concern regarding the reproductive and developmental toxicity based on the characteristics of the SARS-CoV-2 vaccine candidate, reproductive and developmental toxicity studies should be conducted and completed prior to the initiation of a large-scale clinical trial.
 - ✓ In general, study endpoints covering the period from the reproductive/developmental stage C (implantation to closure of the hard palate) through stage E (birth to weaning) should be assessed, in accordance with the WHO guidelines ¹⁶⁾ and the ICH S5 Guideline ¹⁷⁾.
- If a novel adjuvant is used for the SARS-CoV-2 vaccine candidate, safety assessments are required for the adjuvant. Repeated-dose toxicity and reproductive and developmental toxicity of the adjuvant can be assessed as part of the studies with the SARS-CoV-2 vaccine candidate. For genotoxicity, safety evaluation of the novel adjuvant itself should be considered.

2.3. Pharmacokinetics study

- Pharmacokinetic studies are usually not required for infection prophylaxis vaccines. If, however, the vaccine contains a novel substance such as a novel adjuvant, pharmacokinetic studies of the substance may be required.

- For an LNP-mRNA vaccine, DNA vaccine, or recombinant virus vaccine, its postdose biodistribution needs to be assessed. This assessment must be completed prior to the initiation of the first clinical trial in Japan for DNA vaccines and recombinant virus vaccines, or prior to the initiation of a large-scale clinical trial in Japan for LNP-mRNA vaccines.
- For an LNP-mRNA vaccine, DNA vaccine, or recombinant virus vaccine, a biodistribution study with the SARS-CoV-2 vaccine candidate is generally needed. The need for this biodistribution study with the SARS-CoV-2 vaccine candidate may, however, be obviated if the biodistribution of the vaccine candidate can be explained on the basis of the results of biodistribution and clinical studies of another vaccine with the same LNP, DNA plasmid vector, or recombinant virus vector as the SARS-CoV-2 vaccine candidate.

2.4. Disease Enhancement Caused by Administration of SARS-CoV-2 Vaccine

- The disease enhancement possibly caused by administration of SARS-CoV-2 vaccine is referred to as an antibody-dependent enhancement (ADE) or enhanced respiratory disease (ERD). Disease enhancement is believed to be a phenomenon in which antibodies (and/or other substances) produced by administration of vaccine enhance infections or infection-induced inflammation. At present, however, its mechanism of development has not been elucidated. In the development of coronavirus vaccines, animal studies of vaccines against severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) viruses suggest a possibility of these vaccines causing disease enhancement.^{18), 19)} As for preventive vaccines other than coronavirus vaccines, clinical studies of vaccines against RS (respiratory syncytial) virus and dengue virus report fatal and worsened cases to which disease enhancement may have contributed.^{20), 21)}
- Prior to clinical trials, it is necessary to estimate the risk of disease enhancement based on the results of the immunogenic characterization such as the Th1/Th2 balance, SARS-CoV-2 antigen-specific antibody titer and neutralizing antibody titer in the nonclinical pharmacology studies .
- Essentially, a test system with a relevant animal infection model should be introduced to assess the risk of disease enhancement prior to the clinical trials. Considering the current status of COVID-19, however, conducting early phase clinical trials in parallel with the development of the animal model of infection is unavoidable if the risk of disease enhancement has been estimated to be low in the nonclinical pharmacology studies. Even in such a case, the results of the animal study should be reported to the Pharmaceuticals and Medical Devices Agency (PMDA) as soon as possible.
- If a relevant animal infection model becomes available, it is important to assess the risk of disease enhancement by through histopathological examination on the target organ (e.g. lung) in challenge test. It is recommended to assess the risk of disease enhancement using the animal infection model, prior to a large-scale clinical trials.
- If new knowledge regarding how to assess the risk of disease enhancement is obtained in the future, an additional risk assessment by means of the new method should be considered.

2.5. Actions to the Cartagena Act

- To comply with the Act on the Conservation and Sustainable Use of Biological Diversity through

Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003; Cartagena Act), some actions are needed depending on the type or manufacturing method of the SARS-CoV-2 vaccine candidate.

- To conduct a clinical study of a SARS-CoV-2 vaccine candidate that uses a recombinant virus (including replication-incompetent virus) as an active ingredient in Japan, Cartagena type 1 use codes must be laid down and approved in accordance with the Cartagena Act. To manufacture a protein, plasmid DNA, or recombinant virus that is produced with a gene recombination technique in Japan, the manufacturing facility at which a living modified organism(s) is processed must undergo a verification concerning the Cartagena type 2 use.
- When applying for approval of the type 1 use codes, not only meeting the above-mentioned conditions concerning Sections 2.1 to 2.3 of the Cartagena Act, but submission of test results concerning environmental assessment is also required.
- Regarding the actions to the Cartagena Act, scientific advice by PMDA is recommended as early as possible because additional studies might be required to comply with the Act and a certain length of time is required for the reviewing process of the type 1 use codes or the verification procedure concerning the type 2 use.

3. CLINICAL TRIALS IN JAPAN

- The benefit-risk judgement of any SARS-CoV-2 vaccines can differ depending on the situation of each country/region given that the degree of the COVID-19 epidemic, that the virus may undergo mutation according to the geographic/passage conditions, and that the percentage of severe patients with worsened COVID-19 and the background of the worsening is being investigated in various ways. In addition, ethnic differences might affect the efficacy and safety of the SARS-CoV-2 vaccine. There may therefore be a high need of evaluating the efficacy and safety of the vaccine in Japanese subjects by conducting a clinical trial(s) in Japan, even if a large-scale confirmatory trial is conducted overseas to evaluate the disease-preventive effect.
- SARS-CoV-2 vaccine candidates for which pivotal clinical trials are conducted in Japan (vaccine candidates firstly developed in Japan) and those for which pivotal trials are conducted overseas prior to clinical trial in Japan (vaccine candidates that are ahead of development overseas) can differ with respect to the requirements for clinical trials in Japan. In this section, therefore, principles for the two types of vaccine candidate are described separately.
- For principles concerning the evaluation in clinical trials, the summary reports of ICMRA Workshops on COVID-19 Vaccine Development as well as WHO and FDA guidance documents can be used for reference.²²⁾⁻²⁴⁾

3.1. Vaccine Candidates Firstly Developed in Japan

3.1.1. Selection of Dosage

- Multiple dosages should be considered to conduct a clinical trial in Japan, taking into account the routes and schedule of administration, dosages, investigated in nonclinical studies.
- In the present situation in which the relationship between the efficacy of vaccine against COVID-19 and

the antibody titer has not been established, the route of administration, dose and schedule should be determined so that a higher immune response is induced.

- We must assume that in the future a situation in which limited productions of SARS-CoV-2 vaccines must be administered widely to the public can be realized. It is therefore preferable to have a smaller vaccination dose and a fewer administration, and if multiple doses need to be administered, it is preferable to have a shorter dosing interval for rapid acquisition of immunity. Thus, development considering these factors from an early stage is recommended.

3.1.2. Evaluation of Immunogenicity

- Collection data on the SARS-CoV-2 antigen-specific
- c antibody titer, neutralizing antibody titer, cytokine productions, and others should be considered to evaluate the immunogenicity of the SARS-CoV-2 vaccine candidate. The geometric mean concentration (GMC) and geometric mean titer (GMT) of antibodies should be assessed. In late phase clinical trials, it should be considered to, if possible, assess the seroconversion rate or the seroprotection rate of antibodies after a standard value of the antibody concentration or antibody titer is established on the basis of the immunoreactivity results (SARS-CoV-2 antigen-specific antibody titer, neutralizing antibody titer, etc.) from completed clinical trials.
- If a possible disease-preventive marker has been determined from the nonclinical data using animal models in challenge test, it will be useful to perform assessments with the marker when conducting clinical trials in Japan.
- In clinical trials to assess the immunogenicity, information about the incidence of COVID-19 during the observation period should also be collected in an appropriate manner by assuming symptoms possibly related to COVID-19 beforehand, considering the possibility of being able to evaluate the efficacy and safety of the vaccine candidate exploratorily.
- For a recombinant virus vaccine, the immune response to the recombinant virus vector and its effects should be assessed.

3.1.3. Evaluation of Efficacy

- The efficacy of infectious disease preventive vaccines is in principle evaluated using the disease-preventive effect as the primary endpoint. In the current situation in which no surrogate marker for the disease-preventive effect against COVID-19 is known, in principle, clinical trials to assess the preventive effect against COVID-19 must be conducted to evaluate the efficacy of the SARS-CoV-2 vaccine candidate. Other possible key endpoints may include SARS-CoV-2 infection confirmed by a virological or serological method, as well as endpoints concerning the severity of COVID-19 such as arterial oxygen saturation (SpO₂), requirement of oxygen therapy, management with ventilator or ECMO, and death.
- If another SARS-CoV-2 vaccine of which the disease-preventive effect is demonstrated overseas becomes available in Japan, a SARS-CoV-2 vaccine candidate clinically evaluated thereafter may be evaluated for its efficacy in a controlled clinical trial using the efficacy-demonstrated SARS-CoV-2 vaccine as a comparator. In this case, study endpoints should be determined on the basis of the scientific

understanding at that point concerning the mechanism of the disease-preventive effect of SARS-CoV-2 vaccines.

- If in the future the disease-preventive effect of other SARS-CoV-2 vaccines is proved in a clinical trial and an immunogenic marker associated with the disease-preventive effect is confirmed, immunogenicity of the vaccine may be used for reference. For example, efficacy of a SARS-CoV-2 vaccine candidate intended to be developed might be evaluated by confirming its disease-preventive effect in nonclinical studies and its immunogenicity in a Japanese clinical trial.

3.1.4. Evaluation of Safety

- It is required to collect adverse events (AEs) of solicited local reactions (swelling, redness, induration, pain, etc.) and solicited systemic reactions (pyrexia, headache, malaise, myalgia, etc.) observed during the first at least 7 days after administration of the SARS-CoV-2 vaccine candidate as well as all AEs observed during the first at least 28 days after administration; longer periods may however be required depending on the characteristics of the vaccine candidate.
- Adverse events may be collected for at least 7 days after administration of the SARS-CoV-2 vaccine candidate using a method such as (1) calling each subject and hearing the AEs recorded in their Subject Diary or (2) collecting the Subject Diary when the subject visits the study site. The collection of AEs from Day 8 onward must be planned so that information is properly collected; for example, AEs may be collected by calling each subject every week or inputted AE data by each subject on an electronic device.
- Disease enhancement risk should be assessed in clinical trials based on the immunogenic characterization such as the Th1/Th2 balance, SARS-CoV-2 antigen-specific antibody titer, neutralizing antibody titer. When a clinical trial is conducted, it is required to implement an appropriate procedure of informed consent in which subjects have knowledge of the theoretical risk of disease enhancement, perform careful safety follow-up of subjects, and prepare a management system for possible cases of disease enhancement.

3.1.5. Follow-up during the Clinical Trial

- To collect information about the long-term efficacy and safety after administration of the SARS-CoV-2 vaccine candidate, subjects should be followed up at least one year in a clinical trial. A follow-up period longer than one year may be required depending on the characteristics of the SARS-CoV-2 vaccine candidate.
- During the follow-up period, collection of information about the persistence of antibody titer as well as incidence of COVID-19 and AEs including assessment of the disease enhancement risk are required.
- It is preferable to perform the safety follow-up during the clinical trial period also for subjects withdrawing from the trial after vaccination, considering the disease enhancement risk.

3.1.6. Procedure of Clinical Trial

- Clinical trials must be properly conducted in compliance with Good Clinical Practice (GCP).²⁵⁾
- In a first-in-human study, appropriate measures to ensure subjects' safety must be planned and

implemented referring the guidance document, Notification on Revision of Guidance for Safety Assurance in First-in-Human Studies of Drug Development (PSEHB/PED Notification No. 1225-1, dated December 25, 2019)²⁶). In particular, note the following:

- ✓ In a first-in-human study, for risk reduction, it is more appropriate, for example, to evaluate the safety in one or a few subject(s) when administering the vaccine candidate for the first time or administering each stepped-up dose for the first time and then, proceed (i.e., not administering the vaccine candidate to the next subject or at the next dose level until the safety evaluation in one or a few subject(s) is completed). In such a case, prior to administration to subsequent subjects, it is necessary to assess the reactions and AEs experienced by the previous subjects.
- ✓ In the protocol, criteria for step-ups within the clinical trial (regarding, e.g., dose escalation and extension to wider age group) and for suspension/termination of the trial, as well as the procedures, management systems, and responsibilities for these decisions should be predefined.
- When the sponsor of a clinical study chooses study sites, it should make sure:
 - ✓ That each site has facilities that make it possible to respond to emergencies (such as cardiopulmonary arrest, anaphylaxis, cytokine release syndrome, loss of consciousness, seizure and shock) and in the site, physicians who can appropriately respond to those emergencies are deployed, and
- That in case of the occurrence of AE(s) that cannot be managed in the site, it is defined the procedure for transferring the subject to an appropriate external emergency medical institute and for referring the subject to another medical institute or another department in the study site that can manage the AE(s). Actions to take when any signs or symptoms suggestive of COVID-19 is found during the study period should be predefined in the study protocol. Subjects should be given an explanation about those actions.

3.1.7. Necessity of Other Endpoints

- If the vaccine contains novel adjuvant(s) and/or novel excipients, their pharmacokinetics may need to be evaluated.
- For a recombinant virus vaccine or live attenuated vaccine, whether the vaccine strain is shedded from the subject and how to manage the risk of transmission to others should be determined. If the vaccine strain is found to be shedded from the subject, the SARS-CoV-2 vaccine candidate also should be assessed regarding the possibility of transmission to those who have contacted the subject, the genetic stability of the vaccine strain, and the possibility of mutation to a highly virulent strain. In addition, the possibility of shedding and the risk of transmission to others should be explained to subjects and appropriate actions should be taken.

3.1.8. Clinical Trial Design

- The sample size for a clinical trial should be determined to evaluate efficacy and safety of the SARS-

CoV-2 vaccine candidate appropriately, considering the characteristic of the endpoints.

- For a SARS-CoV-2 vaccine candidate produced using innovative technology such as an LNP-mRNA vaccine, DNA vaccine, or recombinant virus vaccine, or for a SARS-CoV-2 vaccine candidate with a novel adjuvant, particularly careful evaluation of its safety is required in clinical trials.
- In principle, any SARS-CoV-2 vaccine candidate should be evaluated in randomized, double-blind, (e.g., placebo-)controlled trials to assess the effect of antibody titer increased by a natural infection of SARS-CoV-2 on postvaccination, to evaluate the safety concerning vaccination, and to assess the incidence of COVID-19 and the risk of disease enhancement.

3.1.9. Evaluation in the Geriatrics, Pregnant Women/Nursing Mothers, and Children

- Considering the high risk of severe COVID-19 in the geriatrics,²⁷⁾ it is recommended to conduct a clinical trial in the geriatrics as early as possible after the vaccination experience in adults (except the geriatrics) has reached a certain level. In late phase of clinical trials, it is recommended to consider inclusion of subjects whose risk of severe COVID-19 may be high (e.g., those who have an underlying disease).
- For infectious disease preventive vaccines, it is possible to initiate clinical trials enrolling women of childbearing potential even if any developmental and reproductive toxicity study has not been conducted; in this case, however, adequate measures to avoid pregnancy need to be implemented with an informed consent about the embryo-fetal risk being uncertain.
- Whether pregnant women/nursing mothers can be enrolled in clinical trials should be determined after the risk of reproductive and developmental toxicity is assessed according to the type of the SARS-CoV-2 vaccine candidate, available nonclinical and clinical study data.
- For children, it is recommended to plan and conduct an appropriate clinical trial after information about the efficacy and safety in adults is obtained.

3.2. Vaccine Candidates that are ahead of Development Overseas

- Even if development precedes overseas and large-scale clinical trials are being conducted to evaluate efficacy and safety overseas, the basic principles concerning their evaluation are the same as those for vaccine candidates first developed in Japan, although in principle, clinical trial must be conducted also in Japan to confirm the efficacy and safety in Japanese subjects. For the clinical trial in Japan, it is recommended to ask scientific advice to the PMDA as early as possible.

3.2.1. Selection of Dosage

- When the clinical development of a SARS-CoV-2 vaccine candidate is further along overseas than in Japan and it can be concluded that the dosage determined overseas are appropriate for the use in clinical trials in Japan, the dosage determined overseas can be used in Japanese clinical trials without conducting a clinical trial in Japan for the selection of the dosage.

3.2.2. Evaluation of Immunogenicity

- Measuring the SARS-CoV-2 antigen-specific antibody titer, neutralizing antibody titer, cytokine

productions, and others should be collected. The (GMC) and (GMT) of antibodies should be also evaluated. It should be considered to, if possible, assess the seroconversion rate or the seroprotection rate of antibodies after a standard value of the antibody concentration or antibody titer is established on the basis of the immunoreactive results (SARS-CoV-2 antigen-specific antibody titer, neutralizing antibody titer, etc.) from overseas trials.

- In clinical trials to assess the immunogenicity, information about the incidence of COVID-19 during the observation period should also be collected in an appropriate manner by assuming symptoms possibly related to COVID-19 beforehand, considering the possibility of being able to evaluate the efficacy and safety of the vaccine candidate exploratorily.
- If the SARS-CoV-2 vaccine candidate has been evaluated in clinical trials overseas, it will be useful to examine the immunoreactive results from a Japanese clinical trial in comparison with the results from overseas trials.
- For a recombinant virus vaccine, the immune response to the recombinant virus vector and its effects should be assessed.

3.2.3. Evaluation of Efficacy

- When a large-scale confirmatory clinical trial of the vaccine candidate is conducted overseas using the disease-preventive effect as the primary endpoint, it may be sufficient to conduct a Japanese clinical trial to confirm the immunogenicity and safety in Japanese subjects without conducting a confirmatory clinical trial in Japan to evaluate the disease-preventive effect in Japanese subjects. When a global development program (multi-regional clinical trial(s)) to evaluate the disease-preventive effect is planned, the efficacy of the vaccine candidate in the Japanese population may be evaluated by participating in the program from Japan.
- If in the future the disease-preventive effect of other SARS-CoV-2 vaccines is proved in a clinical trial and an immunogenic marker associated with the disease-preventive effect is confirmed in multiple trials, immunoreactive results of the vaccine may be used for reference. For example, efficacy of a SARS-CoV-2 vaccine candidate intended to be developed might be evaluated by confirming its disease-preventive protective effect in nonclinical studies and its immunogenicity in a Japanese clinical trial.

3.2.4. Evaluation of Safety

- See Section 3.1.4.

3.2.5. Follow-up during the Clinical Trial

- See Section 3.1.5.

3.2.6. Procedure of Clinical Trial

- When a vaccine candidate is clinically developed in Japan at the same time as overseas, it is necessary to implement a system that makes it possible to obtain safety information from the overseas clinical trials and reflect them to the Japanese clinical trial.

- See Section 3.1.6.

3.2.7. Necessity of Other Endpoints

- See Section 3.1.7.

3.2.8. Clinical Trial Design

- See Section 3.1.8.

3.2.9. Evaluation in the Geriatrics, Pregnant Women/Nursing Mothers, and Children

- See Section 3.1.9.

4. POST-MARKETING ACTIONS

- If a SARS-CoV-2 vaccine has been given marketing approval based on the results of the clinical trials conducted, the marketing authorization holder must take appropriate post-marketing actions for safety based on the safety information obtained from the clinical studies. For example, for the SARS-CoV-2 vaccine candidates currently developing because certain local and systematic AEs have been reported, safety measures at the time of administration and information provision based on these reports are absolutely needed.
- Because the safety information from the clinical studies conducted by the time of approval may be limited, whether the vaccine can be administered widely to the public will be carefully reviewed.
- Following approval, the marketing authorization holder needs to organize a system that makes it possible to properly and rapidly collect the safety information in Japan and overseas and promptly provide it to all medical and other institutions concerned.
- Long-term follow-up results of a large-scale clinical studies can become available after approval. The manufacturer must promptly report those results to PMDA, and publicize them and take necessary actions.

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