Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 4)

Immunogenicity-based evaluation of variant vaccines modified from parent vaccines and booster vaccines with new active ingredients

July 15, 2022

Office of Vaccines and Blood Products
Pharmaceuticals and Medical Devices Agency

1. BACKGROUND

Variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with altered infectivity, transmissibility, antigenicity, and/or pathogenicity have emerged due to viral genome mutations, some of which are designated as Variants of Concern on public health (VOCs). Some VOCs are difficult to neutralize with antibodies induced by SARS-CoV-2 vaccines approved in Japan as of May 2022. Therefore, the development of vaccines to combat such VOCs is required. For that purpose, vaccine developers are trying to tackle variant viruses by modifying existing vaccines and developing new vaccines.

The Pharmaceuticals and Medical Devices Agency (PMDA) issued a document regarding the evaluation of vaccines against such variants titled “Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 1): Evaluation of vaccines against variants”[1] (hereinafter referred to as “Appendix 1”).

However, the landscape surrounding SARS-CoV-2 vaccines has significantly changed since the issuance of Appendix 1.

The main changes in the landscape of SARS-CoV-2 vaccines in the country are as follows:

- Several different types of vaccines, mRNA vaccines, viral vector vaccines, and recombinant protein vaccines, have been approved.
- The target population and application vary among vaccines, with some vaccines expanding their target population to individuals aged 5 years or older.
- More than 80% of the Japanese population has completed the primary vaccination.
- The first additional vaccination (booster dose) is becoming more widespread among the population.
- The second booster dose has been started for the elderly and adults with underlying conditions.

Currently, available information about the protection induced by vaccines and mechanisms of action[2] is as follows:

- Neutralizing antibodies against the Spike protein induced by currently distributed vaccines play a critical role in prophylaxis.
- Factors other than cellular immunity and neutralizing activities of humoral immunity may contribute to the protection by vaccines. These immune responses may influence the durability of vaccines and/or preventive effect of severe disease.
- The protection by vaccines involves a combination of different types of immune responses, and the contribution of serum neutralizing antibodies produced may vary with the type of vaccine.
- The threshold of serum neutralizing antibody levels that reliably predicts the preventive effect of disease onset or progression to severe disease remains unclear.

Several vaccines have become practically available, and the vaccinated population has spread worldwide. Meanwhile, it has been reported that vaccine efficacy wanes over time. Also, as described above, VOCs, against which existing vaccines are less effective, have become prevalent.

In response to this situation, many national governments encourage booster doses with approved vaccines. Epidemiological evaluations have shown that booster doses not only compensate for the efficacy that current vaccines have lost over time but also provide a certain degree of efficacy against new VOCs. These changes in the use of vaccines have led to the following changes in the goals and evaluation of international vaccine development:

- At present, national regulatory authorities evaluate the immunogenicity and efficacy against both ancestral strains and variant strains of SARS-CoV-2 in the evaluation of additional vaccinations.
- SARS-CoV-2 vaccine developers have shifted their target from ancestral strain to variant strains. And, some developers have sought to establish multivalent vaccines containing multiple antigens or antigen genes to accommodate a wide range of variants.
- New developers of SARS-CoV-2 vaccines prioritize developing vaccines dedicated to booster doses for the population vaccinated with approved vaccines.

In light of these changes in social circumstances and the accumulation of scientific knowledge, on January 12, 2022, the International Coalition of Medicines Regulatory Authorities (ICMRA) held an ICMRA COVID-19 Omicron variant workshop[3] to discuss vaccine development, Omicron strains, booster vaccination, and efficacy evaluation using immunogenicity and other issues between medical regulatory authorities worldwide. The US FDA has revised the guidance on its principle on variant vaccines.[4]

In addition, the World Health Organization (WHO) has updated its principle on the efficacy evaluation of SARS-CoV-2 vaccines[5] and the Target Product Profiles[6] (WHO TPP), which describes WHO's recommended requirements for SARS-CoV-2 vaccines.

Based on the review among the relevant regulatory authorities and in light of the updated guidance of overseas and WHO guidance, this document will revise the relevant parts regarding evaluating the quality, efficacy, and safety of vaccines against variants of SARS-CoV-2 in Appendix 1. This document will also present Japan's current view on the application of the immunogenicity-based evaluation of vaccines provided in the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 3): Evaluation of the vaccines based on Immunogenicity"[7] (hereinafter referred to as "Appendix 3") to vaccines with new active ingredients that are developed for additional doses.

2. SCOPE

Part I of this document updates our principle on evaluating the quality, efficacy, and safety of vaccines against variants, considering the situation as of May 2022. Part II presents the principles for the immunogenicity-based evaluation of additional vaccines developed with new active ingredients, taking into account the current SARS-CoV-2 vaccinations. Should there be any discrepancy between this document and the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2" or its appendixes 1 to 3, this document shall take precedence. In this document, a SARS-CoV-2 vaccine currently approved in Japan is referred to as a parent vaccine, and a vaccine against a variant modified from the parent vaccine is referred to as a variant vaccine.

Part I. EVALUATION OF VARIANT VACCINES MODIFIED FROM PARENT VACCINES

3. EVALUATION OF THE QUALITY, EFFICACY, AND SAFETY OF VARIANT VACCINES

3.1. Variant Vaccines Covered by This Document

They are the same as those in Section 2 of Appendix 1. However, multivalent vaccines may also be covered if additional studies are conducted to collect the required information as listed below:

3.2. Quality Data

In principle, as per Section 3 of Appendix 1.

In the development of multivalent vaccines containing multiple antigens or antigen genes as active ingredients, it is necessary to plan additional quality control strategies to ensure the quality assurance of the individual active ingredients at the time of release and through the end of the shelf life.

Points to consider may be related to manufacturing processes and quality control methods that differ from those of the parent vaccine: For example, the manufacturing process for mixing multiple drug substances, control of impurities derived from each drug substance, and the validity of the analytical procedures for individual active ingredients contained in the vaccine product. It will be necessary to establish the appropriate specifications and testing methods. In addition, lot analysis and process validation data should also be collected when modifying a monovalent parent vaccine into a multivalent variant vaccine. The shelf life of multivalent vaccines should be determined basically based on the results of long-term testing. However, the shelf life may be established the same as that of the parent vaccine if the impact of multivalency on stability can be justified based on the data.

3.3. Non-clinical Data

In principle, as per Section 4 of Appendix 1.

In the development of multivalent vaccines, it will be useful to conduct non-clinical trials to compare the multivalent vaccine with its component monovalent vaccines in terms of the expression of the antigen genes and immunogenicity prior to clinical trials. Investigation of a possible increase or decrease in immune responses in such studies may allow prediction of the efficacy and safety of the multivalent vaccine containing multiple antigens or antigen genes in humans.

3.4. Clinical Trial Data on Efficacy

3.4.1. Efficacy evaluation of primary vaccination

Developers must conduct randomized controlled trials in which SARS-CoV-2 vaccine-naive subjects are randomly assigned to receive either the variant vaccine or the parent vaccine to evaluate the efficacy of the variant vaccine for primary vaccination. As far as possible, clinical trials for primary vaccination should include subjects considered eligible according to Section 5 of Appendix 1. If this is not feasible, subjects may be included regardless of history of SARS-CoV-2 infection. In such cases, a prior history of SARS-CoV-2 infection and immunological parameters (presence or absence of anti-SARS-CoV-2 nucleocapsid antibodies and neutralizing antibody titers before vaccination with the investigational vaccine) should be investigated to ensure that they are balanced between treatment groups so that the study design allows interpretation of immune responses.

The principle for selecting doses and intervals for the treatment groups and the availability of plasma samples from previous clinical trials of the parent vaccine are the same as those provided in Section 5 of Appendix 1.

For the efficacy evaluation of variant vaccines for primary vaccination, the variant Geometric Mean Titer (GMT) and immune response rate against the variant should be used as the co-primary endpoints. The superiority or non-inferiority of the variant vaccine to the parent vaccine will be tested for each co-primary endpoint. See Table 1 for specific criteria. Definitions of terms are as follows:

- Variant GMT
  The geometric mean of neutralizing antibody titer against the variant targeted by the variant vaccine
- Immune response rate against the variant
  Proportion of subjects who have immune response at post-vaccination compared to pre-vaccination with respect to neutralizing antibodies against the variant targeted by the variant vaccine

・ Original GMT

The geometric mean of neutralizing antibody titer against the original strain

・ Immune response rate against the original strain

Proportion of subjects who have immune response at post-vaccination compared to pre-vaccination with respect to with respect to neutralizing antibodies against the original strain

In the exploratory assessments, the data on the between-group comparisons of the original GMT and the immune response rate against the original strain as well as the GMT and immune response rates for other VOCs should be collected to help the evaluation of vaccine efficacy.

Table 1. Immune responses to be demonstrated for efficacy evaluation of variant vaccines for primary vaccination

Immune response analysis	Variant vaccine group	Parent vaccine group
Co-primary endpoint: Superiority*[a]	Variant GMT	Variant GMT
Co-primary endpoint: Non-inferiority*[b]	Immune response rate against the variant	Immune response rate against the variant
Secondary endpoint: Non-inferiority*[c]	Variant GMT and immune response rate against the variant	Original GMT and immune response rate against the original strain
Secondary endpoint: Super superiority*[a] (When the co-primary endpoint of variant GMT is tested for normal superiority.)	Variant GMT and immune response rate against the variant	Variant GMT and immune response rate against the variant

*a. It is recommended that the superiority of this co-primary endpoint is set as "super superiority" (the lower limit of the two-sided 95% confidence interval of the GMT ratio is greater than 1.5). When this co-primary endpoint is tested for normal superiority (the lower limit of the two-sided 95% confidence interval of the GMT ratio is greater than 1), the secondary endpoints should be tested for "super superiority."

*b. The non-inferiority margin for the difference in immune response rate should be less than 5%. Alternatively, the superiority of the immune response rate may be tested. (The normal superiority margin of the difference in the immune response rate should be greater than 0%, and the super superiority margin should be greater than 10%.)

*c. The criteria of non-inferiority should be the same as those described in Section 5.1 of Appendix 1.

3.4.2. Efficacy evaluation for booster vaccinations

Developers should conduct randomized controlled trials in which eligible subjects are randomly assigned to receive either the variant vaccine or the parent vaccine (limited to those for which the dosage and administration are approved as additional booster dose in Japan) to evaluate the efficacy of the variant vaccine used for booster doses. In principle, subjects for the clinical trials should be those who have received the primary vaccination with the parent vaccine when evaluating the first booster dose and those who have completed primary and first booster dose with the parent vaccine when evaluating the second booster dose.

In light of the actual situation of vaccination, when actively evaluating the efficacy of cross

immunization of other vaccines, vaccines other than the parent vaccine may be used for the primary vaccination and first booster dose. In such cases, the type of vaccine and timing of vaccination should be properly controlled for the subjects, and the study should be planned in accordance with the objectives of the confirmation.

It is recommended to control for the history of SARS-CoV-2 infection and vaccination of subjects to ensure that they are as homogeneous a population as possible. If this is not possible, a prior history of SARS-CoV-2 infection and immunological parameters (presence or absence of anti-SARS-CoV-2 nucleocapsid antibodies, type of vaccine received, and neutralizing antibody titers before vaccination with the investigational vaccine) should be investigated to ensure that they are balanced between treatment groups so that the study design allows interpretation of immune responses.

For the efficacy evaluation of variant vaccines for booster immunization, the variant GMT and immune response rate against the variant should be used as the co-primary endpoints. The superiority or non-inferiority of the variant vaccine to the parent vaccine will be tested for each co-primary endpoint. See Table 2 for specific criteria.

In the exploratory assessments, the data on the comparisons of the original GMT, variant GMT, GMTs of other VOCs as well as immune response rates against the original strain, variant and other VOCs between clinical trials and between the primary and first booster vaccinations (in the trial of second booster immunization) should be collected.

The immune response rate is generally defined as the proportion of subjects who have post-vaccination neutralizing antibody titers of more than a certain number of times the pre-vaccination titer. However, especially in a trial of booster vaccination, the immune response rate should be defined in advance based on the purpose of booster vaccination where appropriate because definition of the response rate may depend on the objective of the trial and subjects to be compared.

Table 2. Immune responses to be demonstrated for efficacy evaluation of variant vaccines for booster immunization

Immune response analysis	Variant vaccine group	Parent vaccine group
Co-primary endpoint: Superiority*[a]	Variant GMT	Variant GMT
Co-primary endpoint: Non-inferiority*[b]	Immune response rate against the variant	Immune response rate against the variant
Secondary endpoint: Super superiority*[a] (When not set for the co-primary endpoint.)	Variant GMT	Variant GMT

*a. It is recommended that the superiority of the co-primary endpoint is set as “super superiority” (the lower limit of the two-sided 95% confidence interval of the GMT ratio is greater than 1.5). When this co-primary endpoint is tested for normal superiority (the lower limit of the two-sided 95% confidence interval of the GMT ratio is greater than 1), the secondary endpoint should be tested for “super superiority.”

*b. The non-inferiority margin for the difference in immune response rate should be less than 5%. Alternatively, the superiority of the immune response rate may be tested. (The normal superiority margin of the difference in immune response rate should be greater than 0%, and the super superiority margin should be greater than 10%.)

3.4.3. Considerations for immunogenicity measurement

When assessing immunogenicity in clinical trials, not only humor immunity but also cytokine production by $CD8^+$ and $CD4^+$ T cells should be determined using assays with high sensitivity and specificity at least after immunization with the variant vaccine.

In addition, an adequately reliable analytical procedure with validated performance, including accuracy and linearity, should be used to measure neutralizing antibody titers as far as possible. They are measured by an in vitro neutralization test using wild-type viruses or pseudoviruses. When using a pseudovirus, it is necessary in principle to verify the correlation between its neutralization test results and those of the wild-type virus.

Neutralizing antibody titers should be calibrated using the international standard for anti-SARS-CoV-2 antibody provided by the WHO where available.

3.4.4. Considerations regarding the target variant

It is generally assumed that at the time of planning the development of the variant vaccine, the latest VOC is selected as the "variant strain targeted by the variant vaccine candidate" in Tables 1 and 2. However, since the epidemic strain of SARS-CoV-2 changes extremely rapidly, it may be very likely that different VOCs are prevalent at the time of clinical trials and application for approval of the variant vaccine. In addition, there may be cases where the latest VOC at the development planning stage is not selected as the "variant strain targeted by the variant vaccine candidate" as the variant vaccine has broad immunogenicity. In such cases, the GMT and the immune response rate for the latest VOC at the application stage should be evaluated in an exploratory manner.

If the antigen or antigen gene of the variant vaccine under development is changed to that of a sub-linage of the same VOC, it may not be necessary to repeat all the clinical trials described in Section 3.4. again. Therefore, when considering such a change, the strategy for efficacy evaluation should be agreed in advance with the regulatory authority.

3.5. Clinical Trial Data on Safety

As per Section 6 of Appendix 1.

3.6. Actions to the Cartagena Act

As per Section 7 of Appendix 1.

3.7. Points to Consider for Clinical Trials of Multivalent Vaccines

When developing a multivalent vaccine, it is necessary to evaluate the efficacy of individual antigens or antigen genes and the overall safety of the combined vaccine. In multivalent vaccines, cross-reactions, including interference and inhibition by the vaccine components, may occur. Therefore, in clinical trials to evaluate the immunogenicity and safety of multivalent vaccines, an appropriate control group, such as

the parent vaccine group, should be used for comparison. If neutralizing antibody titers against any of the antigens after vaccination with a multivalent vaccine are lower than those obtained with the individual vaccines, the reason and data should be provided to support why the use of the combined vaccine is not problematic for the clinical protection.

Part II. IMMUNOGENICITY-BASED EVALUATION OF BOOSTER VACCINES WITH NEW ACTIVE INGREDIENTS

4. EFFICACY AND SAFETY OF BOOSTER VACCINES WITH NEW ACTIVE INGREDIENTS

This section provides points to consider in confirmatory clinical trials of SARS-CoV-2 vaccines developed for booster doses using new active ingredients (hereinafter referred to as "novel booster vaccine candidates").

The optimal dosage and administration of the new vaccine used in the confirmatory clinical trial should be considered in advance during the required non-clinical trials and a first-in-human clinical trial with reference to the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2".

In this section, it is assumed that novel booster vaccine candidates have the mechanism of action similar to the approved SARS-CoV-2 vaccine, and their efficacy can be evaluated by comparing immunogenicity. If an appropriate control group cannot be used in terms of immunogenicity, for example, due to the mechanism of action significantly different from that of any approved SARS-CoV-2 vaccine, regardless of the immunogenicity-based efficacy evaluation described below, clinical trials should be conducted to evaluate the efficacy in preventing the onset of disease as described in Section 3.1.3 of the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2". In addition, an investigation of whether booster doses can restore efficacy, including preventing effect of severe disease that has waned over time, should be considered.

4.1. Study Design

A confirmatory clinical trial should be conducted as a randomized, active-controlled, double-blind study using the SARS-CoV-2 vaccine already used practically for booster immunization as an active control. Blinding is particularly important if the study is to collect main safety data on the vaccine in the study.

The SARS-CoV-2 vaccine used as the control (active comparator) should be selected with reference to paragraphs 1 to 2 of Section 2. (3) in Appendix 3. The active comparator vaccine should have the approved indication and dosage, and administration appropriate for the intended use and target age population of the novel booster vaccine candidate. In addition, information must be available on clinical efficacy against prevalent VOCs at the time of conducting the study.

4.2. Subjects of Clinical Trials

Subjects suitable for the intended use and target age papulation of the novel booster vaccine candidate

should be included: For example, subjects who have completed the primary vaccination at a given period before the study of first booster dose and those who have completed the first booster dose at a given period before the study of second booster dose.

It is recommended to control for the history of SARS-CoV-2 infection and vaccination of subjects to ensure that they are as homogeneous a population as possible. If this is not possible, a prior history of SARS-CoV-2 infection and immunological parameters (presence or absence of anti-SARS-CoV-2 nucleocapsid antibodies, type of vaccine received, and neutralizing antibody titers before vaccination with the investigational vaccine) should be investigated to ensure that they are balanced between treatment groups, so that the study design allows interpretation of the results with using subgroup analyses.

Additional booster studies should be conducted, as appropriate, in groups of individuals with specific immunological backgrounds who are often ineligible for confirmatory clinical trials.

4.3. Endpoints

[1] Primary and secondary endpoints of immunogenicity

When immunogenicity measures are used as the primary efficacy endpoints in a confirmatory clinical trial, the non-inferiority of the novel booster vaccine candidate to the active comparator vaccine should be tested using the GMT of neutralizing activity against the target SARS-CoV-2 strain and the immune response rate as co-primary endpoints. If the efficacy of the active comparator vaccine is not adequate against the SARS-CoV-2 strain targeted by the novel booster vaccine candidate, a test of the superiority of the novel booster vaccine candidate may be required according to the description in Section 3.4. The immune response rate should be defined in advance based on the purpose of booster vaccination, as described in Section 3.4.2.

In addition to the SARS-CoV-2 strain used as the co-primary endpoint, the neutralizing antibodies against other VOC strains should be measured as secondary endpoints to evaluate the immunogenicity of the vaccine against each of the VOC strains.

Please refer to Section 3.4.3. for points to consider for the evaluation of immunogenicity.

[2] Non-inferiority margins

The lower limit of the 95% confidence interval for neutralizing antibody GMT ratio should not fall below 0.67, and that of the difference in immunity response rate should be less than 10%.

[3] Points to consider for measuring immunogenicity

Consider them with reference to the description in Section 3.4.3.

[4] Considerations regarding the target SARS-CoV-2 strain

It is generally assumed that the latest VOC at the time of the development planning is selected as the "SARS-CoV-2 strains targeted for vaccine development" indicated in Section 4.3.[1]. However, since the

epidemic strain of SARS-CoV-2 changes extremely rapidly, it may be very likely that different VOCs are prevalent at the time of clinical trials and application for approval of the variant vaccine. In addition, there may be cases where the latest VOCs at the development planning stage are not selected as the variant strain targeted by the variant vaccine as the vaccine acquires broad immunogenicity. In such cases, the GMT and immune response rates for the latest VOC at the application stage should be evaluated in an exploratory manner.

4.4. Sample Size

If the safety of the novel booster vaccine candidate has not adequately been evaluated in a reliable clinical trial that includes a sufficient number of subjects, a confirmatory clinical trial should include at least 3,000 subjects from the safety viewpoint.

On the other hand, if, for example, clinical trials have been conducted to evaluate the safety of the novel booster vaccine candidate for primary vaccination, it may be possible to evaluate the safety of a booster doses in a smaller number of subjects. In addition, when individual clinical trials are conducted in the multiple boosting setting, such as when clinical trials for booster doses are conducted separately in young adults and the elderly or when confirmatory studies of first and second booster doses are conducted in parallel, it is not necessary to ensure the number of subjects described above for each individual clinical trial, provided it can be explained that the safety of the novel booster vaccine candidate is consistent in each individual clinical trial.

To determine the final number of subjects to be evaluated in a clinical trial, the properties of the vaccine, subject characteristics, and the study design must be considered.

For other considerations regarding the safety and number of subjects for measuring antibody titers, refer to Section 2. (7) of Appendix 3.

4.5. Confirmation of Vaccine Efficacy and Follow-up of the Durability

In confirmatory clinical trials, it is recommended to follow up the secondary endpoint of the occurrence of clinical events, such as onset of symptomatic COVID-19 or progression to severe disease, to support the immunogenicity-based efficacy evaluation even after the completion of the evaluation of the co-primary endpoints. In addition, a follow-up study of at least one year should be planned to investigate long-term trends in immune response and long-term safety.

The timing of the evaluation of the co-primary and secondary endpoints in confirmatory clinical trials should be planned well in advance based on statistical considerations with reference to the second paragraph of Section 2. (8) in Appendix 3 and should be agreed with the PMDA.

4.6. Safety Evaluation

Information should be collected according to Section 2. (9) of Appendix 3.

4.7. Post-marketing Surveillance, etc.

If the sponsor of a SARS-CoV-2 vaccine candidate acquired marketing authorization on the basis of the data from confirmatory clinical trials using the co-primary endpoint of immunogenicity markers, clinical trials or surveys must be conducted to evaluate the effectiveness of the vaccine on the basis of clinical events after marketing, in which clinical events, including symptomatic disease and progression to severe disease, can be appropriately evaluated in the clinical setting.

These kinds of trials and surveys do not need to be conducted within Japan. However, extrinsic and intrinsic ethnic factors should be taken into account when considering the usefulness of the vaccine in Japan based on the results of the overseas trials or surveys. In addition to clinical trials to compare a novel booster vaccine candidate with an active comparator vaccine based on the primary endpoint of the occurrence of clinical events, as described above, post-marketing database surveys, cohort studies, and case-control studies with test-negative designs are also applicable.

5. ACKNOWLEDGEMENTS

This document has been prepared after hearing from the following experts, and we would like to express our sincere thanks to them:

OUCHI Kazunobu, Professor, Department of Medical Welfare for Children, Faculty of Health and Welfare, Kawasaki University of Medical Welfare
OBA Koji, Associate Professor, Interfaculty Initiative in Information Studies and Department of Biostatistics, School of Public Health, Graduate School of Medicine, The University of Tokyo
OKADA Kenji, Professor, Division of Basic Medical Science and Fundamental Nursing, Fukuoka Nursing College
OKABE Nobuhiko, Director General, Kawasaki City Institute for Public Health
TAKEDA Makoto, Director, Department of Virology III, National Institute of Infectious Diseases
TACHIKAWA Ai, Chief, Division II, AIDS Research Center, National Institute of Infectious Diseases
HAMADA Atsuo, Specially Appointed Professor, Travellers' Medical Center, Tokyo Medical University Hospital
HAYASHI Kunihiko, Director (in charge of education and evaluation) and Vice President, Gunma University
HIRABAYASHI Yoko, Director, Center for Biological Safety and Research, National Institute of Health Sciences
YAMAGUCHI Teruhide, Visiting Professor, Department of Pharmaceutical Sciences, Nihon Pharmaceutical University

---

1) Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 1) Evaluation of vaccines against variants, Office of Vaccines and Blood Products, PMDA, April 5 2021.

2) Developing a framework for evaluation new COVID-19 vaccines. WHO. February 23 2022
3) ICMRA COVID-19 Omicron variant workshop. ICMRA. January 12 2022. https://www.icmra.info/drupal/covid-19/12january2022
4) Appendix 2. Evaluation of Vaccines to Address Emerging SARS-CoV-2 Variants. Emergency Use Authorization for Vaccines to Prevent COVID-19 Guidance for Industry. FDA. March 31 2022.
5) Considerations for Evaluation of COVID-19 Vaccines (Revised). Points to consider for manufacturers of COVID-19 vaccines. Version 30 March 2022. WHO.
6) WHO Target Product Profiles for COVID-19 Vaccines. Revised version April 2022. WHO, April 1 2022.
7) Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 3) Evaluation of the vaccines based on Immunogenicity, Office of Vaccines and Blood Products, PMDA, October 22 2021.