Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 1)
Evaluation of vaccines against variants

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1. BACKGROUND

As a result of SARS-CoV-2 virus gene mutation, virus strain(s) which have different infectiveness, transmissibility, and antigenicity are emerged and detected worldwide (https://www.niid.go.jp/niid/ja/diseases/ka/corona-virus/2019-ncov/10220-covid19-36.html (as of March 31, 2021)). In order to prepare for epidemic of variants which can escape from acquired immunity of people recovered from infectious disease caused by SARS-CoV-2(COVID-19) and neutralizing monoclonal antibodies against SARS-CoV-2, some of the companies which have already granted regulatory approval or emergency use authorization of SARS-CoV-2 vaccine state that they will develop vaccine against these variants (hereafter, "variant vaccine") by modifying existing vaccine.

This document represents basic principles concerning evaluation for the efficacy and safety of these variant vaccines to complement "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2" (September 2, 2020, Office of Vaccines and Blood Products, Pharmaceuticals and Medical Devices Agency) based on the situation as of March 2021. When there is a content overlap between this document and previously published "Principles", this document shall be applied with priority.

It should be noted, however, that although the basic principles presented in this document are based on knowledge at present and overseas guidance on variant vaccine development1) 2) 3) , and have been developed after discussions with external experts on infectious diseases and its prevention vaccines, the principles may change in accordance with new scientific 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 for each investigational vaccine, its benefit/risk will be reviewed taking into account its characteristics.

2. SCOPE

This document outlines the quality, non-clinical and clinical study data that would be required to application of variant vaccines. In principle, this document anticipated to be applied to monovalent vaccine which is developed by sponsor or manufacturer of vaccine that have been already approved in Japan (hereafter, "parent vaccine") in order to gain protection against a variant strain which is different from a SARS-COV-2 strain used to develop parent vaccine, and is intended to replace the parent vaccine. In addition, manufacturing process and control is the same or very similar to those for the parent vaccine. Thus, individual additional consideration may be necessary to develop other variant vaccines including multivalent vaccines.

This document is based on assumption that there is a high possibility that protection of SARS-CoV-2 vaccine is derived mainly from neutralizing activity against SARS-CoV-2 of antibodies elicited by vaccination.

One of the reasons of such assumption is that collected science knowledge such as non-clinical study on correlate between protection from SARS-CoV-2 and IgG antibody from primates infected with SARS-CoV-2[4)], observational study on relationship between antibody against SARS-CoV-2 Spike (S) protein and SARS-CoV-2 infection in the UK[5)], and reanalysis of clinical study data of vaccine against SARS-CoV-2 which has already been put into practical use and anti-spike protein IgG antibody titer[6)] has been revealing the relationship between neutralizing activity of antibody against SARS-CoV-2 and protective effect of vaccine. It should be noted, however, correlate between protective effect of vaccine and immunogenic marker is not established at present, and threshold of immunogenic reaction which can be used to predict disease-preventive effect is not identified, and therefore the principles of this document is applied to development of variant vaccine as long as the vaccine is determined to have the same mechanism of action, route of administration and similar immunogenic profile as parent vaccine.

In addition, variant which is the target of the development should be decided by developer or manufacturer based on overall consideration on epidemiology of variants, virologic data, future epidemic prediction of variant strain(s), immunologic data and guidance on selecting strain(s) published by international organization.

3. QUALITY DATA

Submission data on quality for regulatory approval should include documents on manufacturing process and specifications of variant vaccine, documents on stability as well as documents to describe that manufacturing process of the vaccine is the same or very similar to that of parent vaccine and to describe difference between them. Applicants should consider to include the followings in application documents:

- Information on difference between variant vaccine and parent vaccine (e.g. different points from parent vaccine such as DNA template, virus seeds)
- Study data which can indicate that key quality attributes (e.g. purity, content) of variant vaccine are the same as those of parent vaccine with the same quality control of those of parent vaccine. Any deviation would require adequate scientific or clinical justification.
- Data to show consistency of manufacturing process (e.g. characteristic analysis, In-process control data and lot analysis of active substance and the final product)
- Update of quality control strategy of variant vaccine after the approval of parent vaccine (e.g. specification, impurities, excipients and container closure system)
- Stability data of variant vaccine at the time of application and plan to further collect stability data

In principle, the same storage conditions and a shelf life as parent vaccine are applied to variant vaccine, based on the assumption that the quality attributes are the same as those of parent vaccine. Applicant should provide justification of the storage conditions and the shelf life by demonstrating the similarity between parent and variant vaccines based on the stability data of active substance and the final product (the long-term stability data and the accelerated stability data) gained at the time of application of variant vaccine. Also, stability testing of active substance and the final product of variant vaccine should be continued properly after the approval and study data which covers approved shelf life should be promptly submitted to Pharmaceutical and Medical Devices Agency (PMDA).

4. NONCLINICAL STUDY DATA

In general, non-clinical pharmacology, toxicology, and pharmacokinetic studies are not required to conduct in development of variant vaccine, and necessity is determined based on document regarding data on parent vaccine or vaccine from the same platform as parent vaccine (other vaccine using the same technology as parent vaccine, including lipid nanoparticle (LNP), DNA plasmid vector and recombinant viral vector). However, regarding attenuated live vaccine, the proliferative may differ between parent vaccine and variant vaccine because of antigen modification, so the principles above may not be applied.

Challenge test using animal model of variant vaccine may support to interpret clinical trial data. The study data are especially useful when it is difficult to enroll subjects who had not acquired immunity against SARS-CoV-2 to clinical trial, and when it is difficult to interpret obscure immunogenicity data of clinical trial.

5. CLINICAL TRIAL DATA ON THE EFFICACY

Regarding the clinical trial, both or one of the following designs should be conducted depending on the expected uses of variant vaccine; in the case where variant vaccine is administrated to the person who has no vaccination history of SARS-CoV-2 vaccines including parent vaccine and no infection history of SARS-CoV-2 (hereafter, "initial immunization"); in the case where variant vaccine is administrated to the person who already got the vaccination of parent vaccine (hereafter, "booster immunization").

When there are enough serum samples gotten from the clinical trial of parent vaccine, it is possible to use these samples as control group of the clinical trial below under the condition that the population to compare is sufficiently similar, if the same assay is used for parent and variant vaccine to investigate neutralizing antibody titer, and the dosage and administration investigated in the clinical trial of parent vaccine is the same as those of variant vaccine.

5.1 Administration of variant vaccine as Initial Immunization

In the clinical trials, subjects are randomized to variant vaccine group and parent vaccine group, the same dosage and dosing interval as approved dosage and administration of parent vaccine are used for each vaccine in principle, and schedule of taking serum is established based on clinical trial data conducted for development of parent vaccine.

When assessing efficacy, non-inferiority of immunogenicity against variant in variant vaccine group to immunogenicity against wild strain in parent vaccine group should be statistically assessed using the pre-defined non-inferiority margin, and, for this end, clinical trial should be ensured to have enough power to this assessment. Primary endpoints are seroconversion rate of neutralizing antibody (defined as proportion of subjects whose neutralizing antibody titer is increased by more than 4 times after vaccination) and geometric mean titer (hereafter, "GMT") of neutralizing antibody.

In principle, non-inferiority margin is defined -10% as the difference of seroconversion rate of neutralizing antibody and 0.67 as GMT ratio, and each is assessed in comparison to the lower bound of the 95% confidence interval. If another value is used as the non-inferiority margin, a justification according to individual cases should be explained.

When vaccine efficacy of parent vaccine is lower than 60%, more stringent non-inferiority margin can be required.

In addition, neutralizing antibody titer against wild strain in the serum of variant vaccine recipients and neutralizing antibody titer against variant in the serum of parent vaccine recipients should be assessed as secondary analysis. When comparing neutralizing antibody titer, reverse cumulative distribution curve should be made.

5.2 Administration of variant vaccine as Booster Immunization

In clinical trial that administer variant vaccine as booster immunization, immunogenicity of booster immunization against variants is compared to that of initial immunization against wild strain.

It is recommended that subjects to be vaccinated with variant vaccine should be those who participated in the clinical trial of parent vaccine, received parent vaccine according to approved dosage and administration and whose data of neutralizing antibody titer were obtained at initial immunization. If it is impossible, careful considerations shall be given to enhance comparability, such as collecting data of neutralizing antibody titer at initial immunization from the group whose age, gender and underlining disease, etc. are consistent with variant vaccine group.

Regarding primary endpoint of clinical trial and its statistical assessment, secondary analysis, and other assessment specifications, refer to Section 5.1.

5.3 Considerations in Conducting Clinical Trial

The above clinical trial is conducted in single age group (for example, 18-65 years of age, the age group used in the clinical trial of parent vaccine), and its result can be extrapolated into other age groups that are approved for parent vaccine.

Regarding a clinical trial to assess variant vaccine as initial immunization, if it is difficult to conduct a clinical trial in people who are not immune to SARS-CoV-2, due to the increase of SARS-CoV-2 vaccine recipients and SARS-CoV-2 ex-infected person, it needs to be explained that the result of clinical trial is interpretable, by additionally considering how immune status of subjects could affect the efficacy of variant vaccine.

If overseas trials like above-mentioned trial conducted demonstrated that immunogenicity and immunogenicity profile of variant vaccine were similar to those of parent vaccine, and if no particular concern about efficacy and safety of parent vaccine was identified in Japanese clinical trial for parent vaccine which investigated immunogenicity and safety in Japanese population, additional Japanese clinical trial is considered unnecessary. When applying for approval of variant vaccine without conducting Japanese clinical trials, it should include justification for invocation of overseas trials regarding immunogenicity in Japanese.

6. CLINICAL TRIAL DATA ON THE SAFETY

Regarding the safety assessment, it is required to collect adverse events (AEs) of solicited local reactions and solicited systemic reactions observed during the first at least 7 days after immunization, serious AEs observed during the confirmation period of immunogenicity as well as other AEs. If any signals related to the safety are detected in the clinical trial, further safety assessment based on pharmacovigilance data of parent vaccine etc. and, according the situation, large safety study of variant vaccine can be needed.

For variant vaccine being developed, a plan to collect safety information for a long term should be required, including data collection of Japanese and foreign AEs after the market launch. Regarding this plan, together with protocols of clinical trials, scientific advice by PMDA is recommended as early as possible.

7. ACTIONS TO THE CARTAGENA ACT

If some actions are needed in the development of parent vaccine 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), scientific advice by PMDA is recommended as early as possible because additional actions can be needed in the development of variant vaccine.

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