Provisional Translation (as of May 2024) *

# Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 5)
## Quality data required for the approval review of changing a strain in the vaccine for which the manufacturing process is well established
## (Early consideration)

May 29, 2024

Office of Vaccines and Blood products,
Pharmaceuticals and Medical Devices Agency

1. Background

On May 5, 2023, the World Health Organization (WHO) declared the end of the Public Health Emergency of International Concern (PHEIC) caused by the outbreak of the novel coronavirus (SARS-CoV-2) infectious disease (COVID-19). In Japan, on May 8, 2023, the classification of COVID-19 under the Infectious Diseases Control Act was downgraded from Class 2 to Class 5 infectious disease. [1)] In addition, pharmaceutical process related to drugs for COVID-19 are now generally handled in the same manner as other drugs. [2)] Furthermore, the special exception for temporary vaccination campaign of SARS-CoV-2 vaccine ended on March 31, 2024.

However, new SARS-CoV-2 variant strains with altered infectivity and transmissibility continue to emerge, causing outbreaks. Furthermore, even people who have already been infected with SARS-CoV-2 may be reinfected, and some patients have been reported to have the sequelae of COVID-19 (so-called Long COVID). Therefore, from fiscal year 2024 onwards, routine vaccinations campaign (Category B diseases specified in Immunization Act) will be administered to the elderly and others at-risk population aged 60 and older with the aim of reducing the number of serious cases by preventing disease progression in individuals. In the interest of public health, there is a social demand for a continuous supply of effective SARS-CoV-2 vaccines against epidemic strains.

On May 8, 2023, the International Coalition of Medicines Regulatory Authorities (ICMRA) reached a consensus among regulators on the use of a "platform approach" for updating of SARS-CoV-2 vaccine composition (coding sequence/strain) to align to a new variant (so-called strain change). [3)]

At that time, it was recognized that there was sufficient experience with strain changes in SARS-CoV-2 vaccines manufactured and distributed internationally, and to rapid strain changes the following regulatory procedural requirements were agreed upon:

(1) At the time of application, it is acceptable to submit only the necessary quality and non-clinical study data.
(2) Other information on quality data and real-world data on immunogenicity, efficacy and safety will be required to be collected after approval.

This consensus was reaffirmed at the ICMRA/WHO Workshop on International Perspectives on Strain Modification of COVID-19 Vaccines held on 26 and 27 February 2024 (ICMRA/WHO WS), [4] and the discussions among regulatory authorities continue to focus on harmonization of data submission requirements.

When applying for COVID-19 vaccine strain change under this consensus, it is essential to establish a robust manufacturing process for strain changes in the vaccine. In order to establish the robust manufacturing process, the impact of strain changes on the quality characteristics of the vaccine should be thoroughly evaluated, and manufacturing process, the specifications, and the analytical procedures should be established for strain changes.

Based on this consensus, this document outlines the requirements for submitting an application for partial changes to change a strain of SARS-CoV-2 vaccine whose manufacturing process has been well established in Japan. Specifically, it categorizes applications into those eligible a expedited review process (the approval application with rapid process for strain changes) and those subject to a standard review process(the approval application with standard procedure for strain changes). This document provides further details on the quality requirements for each type of review process.

Please note that the concepts in this document were developed based on scientific knowledge and international trends as of April 2024, and may be subject to change due to future changes in these areas.

## 2. The application types for strain changes

In accordance with the relevant notice, [5] the vaccines eligible for the approval application with a expedited review process for strain changes are those already approved in Japan, for which the strain changes have been accepted in a previous application. In addition, the vaccine should be one whose quality and safety are likely not to be affected by the strain changes, and its immunogenicity can be predicted through non-clinical trials. Therefore, it is assumed that a robust manufacturing process has been established, even when the strain is changed. Regarding the SARS-CoV-2 vaccine, discussions on selecting strains in 2022 (Omicron strain BA.1 and BA.4/5) and 2023 (Omicron strain XBB.1.5) were held around April to June, and the vaccine supply began around September to October. Considering the previous strain changes, this document envisions that the SARS-CoV-2 vaccine eligible for expedited review process for strain change are those for which the applicant should be able to manufacture a prototype of the candidate vaccine using established manufacturing process before the strain of the year is selected. The applicant should also have initiated non-clinical pharmacology studies to demonstrate that candidate vaccines indicate adequate immunogenicity against the prevalent strain. After selecting a strain of the year, the applicants should be able to start supplying within 3-5

months. If such a vaccine is available, the applicant should submit the approval application with expedited review process for strain changes. On the other hand, the applicant should apply the approval application with standard procedure for strain changes, if the established manufacturing process needs to be changed due to the strain changes (excluding minor changes of manufacturing parameters, etc.), or if unintended changes in quality attribute are observed due to the strain changes. This is because it will be necessary to evaluate the comparability of the drug substance, drug product, or their intermediates (hereinafter referred to as "products") before and after the changes, making it difficult to obtain necessary development data and complete regulatory procedures within the expected rapid review period. In this case, an application for the strain changes would normally need to be submitted after the necessary results for approval review have been obtained, and would be reviewed within the standard review process.

For SARS-CoV-2 vaccines undergoing a strain change for the first time, or for which there are concerns about the impact on quality or safety of the strain changes, the following documents can be referred to:

- 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
- 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, Office of Vaccines and Blood Products, PMDA, July 15, 2022

This document is written with mRNA vaccines and recombinant protein vaccines in mind. For other types of SARS-CoV-2 vaccines, this document may be used as a reference; however prior consultation with the Pharmaceuticals and Medical Devices Agency is required.

3. Quality data required for the approval review of strain changes and necessity of GMP inspection application

The table below shows the quality data required for the approval review and necessity of GMP inspection application for expedited or standard revies process for strain changes.

Table Test results related to quality required for approval of application for strain change and necessity of GMP inspection application

| | Expedited revies process for vaccines strain changes | Standard review process for vaccines strain changes |
|---|---|---|
| Control of materials | The characterization and specification data of template DNA, cell bank and viral seed for new strain. | The characterization and specification data of template DNA, cell bank and viral seed for new strain. |
| Characterization | At least 1 batch. (A1) | At least 1 batch. (B1) |
| Batch analyses | In principle, at least 3 batches of the manufacturing scale of production. (A2) | at least 3 batches of the manufacturing scale of production. (B2) |
| Long-term stability | In principle, post-approval stability protocol for at least one batch for which manufacture and storage are representative of the manufacturing scale of production (A3)<br>The shelf life of the product before the strain change can be applied to the product after the strain change. | A minimum of 6 months stability data of at least 3 batches for which manufacture and storage are representative of the manufacturing scale of production (B3)<br>If no difference in stability is observed before and after the strain change, the shelf life of the product before the strain change can be applied to the product after the strain change. |
| GMP inspection | Not required (A4) | In principle, required |

(Annotation.)

- A1: The characterization of the product after the strain change (elucidation of structure and other characterization, and impurities) should be compared with the complete characterization data of the product before the strain change (except for those properties not affected by the strain change). If there is concern that the strain change may impact quality attributes, such as a trend observed in the characterization of the product after the change that is different from that before the change, the submission of data for at least three batches may be required.
- A2: To confirm consistency of production before and after the strain change, the data of the manufacturing scale of production is required. For mRNA vaccines, at least one batch data of the manufacturing scale of production can be acceptable if the consistency of production before and after the strain change can be explained by the prior knowledge from the product before strain change.
- A3: One batch is acceptable on the assumption that there is no concern about an effect on stability from lot to lot or before and after strain change on the result of long-term stability studies from at least three batches at the time of initial approval and at least three batches at the time of approval of a previous strain change.
- A4: If a GMP inspection is deemed necessary, the applicant should submit the approval application with standard revies process for strain changes.
- B1: The characterization of the product after the strain change (elucidation of structure and other characterization, and impurities) should be compared with the full characterization data of the product before the strain change (except for those properties not affected by the strain change). For characterization that are expected to vary from lot to lot, the analysis data of multiple lots may be required.
- B2: To confirm consistency of production before and after the strain change, the data of the manufacturing scale of production is required.
- B3: Batches of the manufacturing scale of production are also acceptable.

(Other notes)

- When validated analytical procedure parameters, reagents, or reference materials are changed with the strain change, revalidation of analytical procedure is required. When the specification acceptance criteria are changed, documents related to the rationale for the criteria are required.
- If there are multiple manufacturing sites, data is required for each manufacturing site. However, if the comparability of products between manufacturing sites can be ensured even after strain change, approval can be obtained with data from one manufacturing site, and data from the remaining manufacturing sites can be verified by the marketing authorization holder.

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1) Ordinance to Partially Amend the Enforcement Regulations of the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases. Ministry of Health, Labour and Welfare Ordinance No. 74, dated April 28, 2023
2) Review of Pharmaceutical Procedures Following the Change in the Legal Status of COVID-19 under the Infectious Diseases Law. PSEHB/PMDA Notification No. 0428-4, PSEHB/ELD Notification No. 0428-1, dated April 28, 2023
3) ICMRA COVID-19 Omicron variant workshop（https://icmra.info/drupal/en/covid-19/8may2023）
4) The ICMRA/WHO workshop on: Global perspectives on COVID-19 vaccines strain update Alignment on timing and data requirements（https://icmra.info/drupal/covid-19/26_27february2024）
5) Regarding the Handling of Changes to COVID-19 Vaccine Strains. PSB/PMDA Notification No. 0523-1, PSB/CND Notification No. 0523-3, dated May 23, 2024