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Guidelines for the Development of Recombinant Virus Vaccines for Infectious Disease Prevention

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Chapter 1: General Provisions

1. Introduction

Thanks to advances in recombinant DNA technology and biotechnology, the development of recombinant viral vaccines for the prevention of infectious diseases (hereinafter referred to as "recombinant viral vaccines") has been progressing. Some recombinant viral vaccines incorporate genes encoding antigens that were not originally present in the virus, which are designed to express these antigens in human cells, thereby aiming to induce an immune response similar to that of a natural viral infection. Furthermore, for viruses with high pathogenicity that have made the development of live attenuated vaccines difficult using conventional techniques, some recombinant viral vaccines are engineered to enhance safety by modifying characteristics such as replicative capacity and cell/tissue tropism, thereby reducing pathogenicity. Thus, recombinant virus vaccines are being developed with the expectation of offering advantages in both efficacy and safety.

For infectious diseases where prevention through vaccination is anticipated, humans have often been exposed to the wild-type viruses of these diseases, accumulating clinical and academic knowledge about them. In the development of conventional live attenuated virus vaccines, researchers have utilized the knowledge of the wild-type viruses from which the vaccine strains are derived to comparatively evaluate the characteristics of the attenuated vaccine strains, such as their replication capacity and cell/tissue tropism. On the other hand, in the development of recombinant virus vaccines, the genes of the original wild-type viruses are artificially modified, which may result in different cell or tissue distribution and different safety profiles compared to the original viruses. Furthermore, clinical experience with recombinant virus vaccines remains limited at present, and future studies such as clinical trials may uncover new insights into their characteristics. Considering the above, it is important to carefully evaluate the quality, efficacy, and safety of recombinant virus vaccines from a perspective different from that of conventional live attenuated virus vaccines.

2. Purpose

These Guidelines summarize the principles and considerations regarding quality, efficacy, and safety to facilitate the smooth development of recombinant virus vaccines. These Guidelines complement Guidelines for Nonclinical Studies of Vaccines for Infectious Disease Prevention (Revised) (PSB/PED Notification No. 0327-1 issued by the Director of

the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, dated March 27, 2024), Guidelines for Clinical Studies of Vaccines for Infectious Disease Prevention (Revised) (PSB/PED Notification No. 0327-4 issued by the Director of the PED, PSB, MHLW, dated March 27, 2024), and Guidance on Clinical Evaluation of Travelers' Vaccines, etc. (PSEHB/ELD Notification No. 0407-1 issued by the Director of the Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated April 7, 2016). These Guidelines have not been prepared for pandemic vaccines that require prompt development to respond to the global epidemic of new infectious diseases; for the development of pandemic vaccines using recombinant viruses, Guidelines for the Development of Prototype Vaccines in Preparedness for Pandemic Influenza (PFSB/ELD Notification No.1031-1 issued by the Director of the ELD, PFSB, MHLW, dated October 31, 2011) and Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Office of Vaccines and Blood Products, Pharmaceuticals and Medical Devices Agency, dated September 2, 2020) may be helpful.

In addition, it should be noted that the present Guidelines have been reviewed based on the current scientific level and may be changed according to new findings in the future or scientific progress.

3. Scope

These Guidelines are applied to recombinant virus vaccines for the prevention of infectious diseases that contain viruses generated using recombinant DNA technology to modify properties such as antigenicity, proliferation, or cell/tissue tropism (hereinafter referred to as "recombinant viruses") as active ingredients.

Note, however, that vaccines that contain genetically engineered viruses inactivated by a chemical method such as formalin as active ingredients are not within the scope of these Guidelines. Vaccines that contain genetically engineered viruses with properties and genetic compositions considered to be equivalent to those of naturally occurring viruses (natural occurrences) as active ingredients are not also within the scope of these Guidelines.

4. Definitions

(1) "Recombinant virus" is a virus prepared using recombinant DNA technology to modify its properties such as antigenicity, proliferation, and cell/tissue tropism.

(2) "Recombinant Virus Vaccine" shall mean a vaccine containing a recombinant virus as an active ingredient. Recombinant virus vaccines include so-called viral vector

vaccines, vaccines with viral vectors into which the target antigen genes are inserted.

(3) "Original virus" refers to the virus from which a recombinant virus is derived. This includes wild-type viruses, viruses obtained through passaging wild-type viruses, and viruses such as viral vectors before the insertion of target genes, and can be used as comparators to characterize the active ingredients of recombinant virus vaccines.

(4) "Proliferation" refers to the process of viruses that the virus enters into cells, viral proteins are synthesized, the viral genome is replicated, virus particles are formed, and as a result, progeny virus particles are increased.

(5) "Replication-incompetent recombinant virus" is a virus in which the genes required for proliferation have been deleted by recombinant DNA technology. For replication-incompetent recombinant viruses to replicate, genes, proteins, etc. necessary for the proliferation of the viruses must be supplied from other helper viruses, cells, etc.

(6) "Replication-competent recombinant virus" refers to a recombinant virus that is not a replication-incompetent recombinant virus.

(7) "Replication-competent recombinant virus vaccine" is a vaccine containing a replication-competent recombinant virus as an active ingredient.

(8) "Target genes or the like" refer to the entities essential for the indications of the product or the genes that are to alter the original virus characteristics. They include not only base sequences coding antigen proteins but base sequences that do not encode antigens but are involved in changing the virus characteristics.

(9) "Master Virus Seed" (hereinafter referred to as "MVS") refers to an aliquot of a homogeneous suspension obtained by culturing a particular recombinant virus in a certain manner and stored under appropriate conditions.

(10) "Working Virus Seed" (hereinafter referred to as "WVS") refers to an aliquot of a homogeneous suspension obtained by culturing MVS in a certain manner and stored under appropriate conditions.

(11) "Seed Lot System" is a management system for virus seeds of MVS and WVS designed to ensure consistent production of uniform preparations. Virus seeds are controlled through defined cultivation methods, passage numbers, storage conditions, and specifications, for the purpose of supplying produced preparations at a constant quality during an extended period.

(12) "Cells for manufacturing" are cells in which recombinant viruses can proliferate and that are used when manufacturing recombinant virus vaccines.

5. Principles on the development

At present, clinical experience with recombinant virus vaccines for disease prevention is less extensive than that for conventional inactivated vaccines, and new findings in humans may be accumulated in the future clinical use. Furthermore, considering the possibilities that recombinant viruses have characteristics not reported in the original viruses and that when recombinant viruses are shed from the vaccine recipients, the shed recombinant viruses will be transmitted to third parties, careful development is required while fully understanding the characteristics of the recombinant viruses and ensuring the safety of not only the vaccine recipients but also close relatives and other third parties, considering the possibility of infection from close distances or with contacts.

It is desirable to advance the development of recombinant virus vaccines for practical use in Japan by taking into account the characteristics of the recombinant viruses, analyzing the risks/benefits based on the expected use, and confirming the opinions of the regulatory authorities from the early stages of development; developers are advised to utilize clinical trial consultations, etc. offered by the Pharmaceuticals and Medical Devices Agency as necessary.

Chapter 2: Outlines of Recombinant Virus Vaccines, Development Histories, etc.

An outline of the recombinant virus vaccine under development and other information such as development history are important for planning quality, non-clinical, and clinical evaluations. Aspects of a development program such as sufficiency of the planned evaluations and an evaluation policy are to be determined by thoroughly understanding the characteristics of the recombinant virus vaccine under development and taking into account the expected usefulness and predicted risks; it is therefore advisable to start consultations with the regulatory authorities from the early stages of development as much as possible about the evaluation policy dependent on the characteristics of the recombinant virus vaccine to advance the development for practical use in Japan.

Before starting clinical trials in Japan, the developers should describe, in documents related to clinical trials such as Investigator's Brochure, an outline of the current preventive or therapeutic treatments for the target infectious disease, and the expected usefulness and predicted risks determined from the characteristics of the recombinant virus vaccine under development. The characteristics of the recombinant virus vaccine should be described taking into account "1. History of the development of recombinant virus" and "2. Properties of recombinant virus" below.

When there is a precedent development of another recombinant virus vaccine that is based on the same original virus as the recombinant virus vaccine under development, the

development information on the precedent vaccine should be collected as much as possible, and the collected information should be provided in the Investigator's Brochure, etc. as supplemental information on the efficacy and safety of the recombinant virus vaccine under development at the start of the clinical trial.

1. History of the development of recombinant virus

(1) Characteristics and the selection of the recombinant virus and the original virus

While replication-incompetent viruses with low pathogenicity are generally expected to be used as recombinant viruses, replication-competent viruses and viruses with broad cell/tissue tropism may also be used. Furthermore, the following viruses may be used as the original viruses in some cases: viruses that are prone to mutation during culture; viruses for which recombination events such as gene reassortment have been reported to occur in nature; viruses with latent infectivity; and viruses for which immune response in nonclinical animal species is unknown. The rationale for developing a recombinant virus vaccine using the selected viruses should be provided, showing the potential risks predicted from the characteristics of both the recombinant virus and the original virus and explaining the expected benefits of the vaccine.

(2) Reasons for selecting the target genes or the like

The reasons and purposes for selecting the target genes or the like and their functions should be explained. When genes for activating the immune response have been introduced, not only the benefits but the risks of unintended immune responses should be explained.

(3) Information on genetic engineering used for the production of recombinant viruses

Regarding the genetic manipulations used for producing recombinant viruses, the developer should clarify their purposes and explain the intention of each manipulation step using flow charts, etc.

2. Properties of recombinant virus

Understanding the structure, physicochemical properties, and biological properties of the recombinant virus used for the vaccine under development is important for the pharmacological and toxicological evaluation of the vaccine and for planning clinical trials.

The developer should explain the properties of the recombinant virus on the basis of the following analyses of the recombinant virus and literature information on the original virus.

(1) Structure of recombinant virus

1) Structure of recombinant virus particle

The structure of the recombinant virus particle is important information for quality

evaluation. The developer should explain the differences from the original virus. When any intended modification is made for the structure of the recombinant virus particle, the reason and rationale for it should be explained.

2) Gene sequence

The purpose of the gene modifications performed to produce the recombinant virus and how they are performed are important information for quality evaluation. When mutations by gene modifications have been introduced to the target genes or the like, the purpose of the mutations should be explained.

In principle, the entire base sequence of the recombinant virus should be analyzed to confirm that an expression construct has been constructed as intended.

(2) Physicochemical properties of recombinant virus

The physicochemical properties of the recombinant virus provide important information for considering how to handle the recombinant virus vaccine in clinical practice. Physicochemical properties that should be clarified include the following:

1) Stability assuming accidental leakage, etc.
2) Inactivating conditions (e.g., those for the heating method or the use of disinfectants for inactivating the recombinant virus)

(3) Biological properties of recombinant virus

Biological properties of the recombinant virus are important information to understand the efficacy, safety, and transmissibility of the recombinant virus vaccine. Biological properties that should be clarified include the following:

1) Cell/tissue tropism

When a gene related to the cell/tissue tropism of a recombinant virus is modified, it should be confirmed that the intended characteristics are obtained. Assessing the replication ability of the recombinant virus and the presence or absence of gene expression in cells using multiple kinds of appropriate human-derived cells provides useful information for understanding the cell/tissue tropism of the recombinant virus in humans.

2) Species specificity

The ability of the original virus to replicate in the animal species and animal-derived cells used for nonclinical studies should be explained using literature or other sources. To justify the appropriateness of animal species selection in nonclinical studies, it is useful to: Confirm the replication ability of the recombinant virus in the selected animal species or their derived cells, for replication-competent recombinant viruses; or verify the expression of the target gene in the cells, for

replication-incompetent recombinant viruses.

3) Expression of proteins in cultured cells

Expression of the recombinant virus antigen in cultured cells should be confirmed. Furthermore, when the characteristics related to the localization and/or extracellular secretion of the expressed target antigen protein are altered, it should be confirmed that the intended characteristics have been obtained.

When a gene with a specific purpose other than antigen (such as granulocyte-macrophage colony-stimulating factor [GM-CSF] gene) is introduced into a recombinant virus, the biological activity and expression level of the target protein that the recombinant virus expresses should be confirmed and its effect on the living body should be explained.

4) Cytotoxicity

When a gene related to the cytotoxicity of a recombinant virus is modified, it should be confirmed that the intended modification has been made. Evaluating the cytotoxicity using the recombinant virus with selected multiple appropriate kinds of human-derived cells may provide useful information for justification of the modification.

5) Pathogenicity

Regarding the original virus, its pathogenicity when it infects humans and animals should be explained using literature, etc. Regarding the recombinant virus, when a pathogenicity-related gene is modified, its impact including the possibility of reversion of pathogenicity should be explained. When a recombinant virus developed in Japan has been administered to humans in overseas clinical studies, the pathogenicity of the recombinant virus in humans should be explained taking into account the results from those studies.

6) Possibility of emergence of mutant viruses

Whether the original virus likely undergoes homologous recombination or gene reassortment (hereinafter referred to as "homologous recombination, etc.") with other viruses should be explained using literature, etc. Evaluation should be conducted regarding whether the replication-competent or -incompetent recombinant virus likely mutates as a result of homologous recombination, etc. with other viruses in the intended clinical use. For this evaluation, information such as the sequence homology between the recombinant virus and other viruses and the biodistribution relationship between the recombinant virus and other viruses may be helpful.

The possibility that the original virus may mutate during the process of replication in the human body should be explained using literature, etc. Evaluation should be conducted regarding whether a replication-competent recombinant virus may mutate during the process of replication in the vaccine recipients, and as a result, its characteristics such as antigenicity, replication competence, and cell/tissue tropism may be altered.

If, as a result of the evaluation, there is a concern that mutated viruses may emerge, nonclinical or clinical studies should be considered taking into account the requirement to evaluate the frequency, replication competence, pathogenicity, etc. of the mutated viruses.

7) Responses to undesirable properties of original virus

Although using viruses with undesirable properties such as chromosomal integration potential and latent infectivity as original viruses should be avoided in principle, recombinant viruses with these properties deleted by genetic engineering may be useful in some cases. In such cases, the lack of these properties in the recombinant virus should be confirmed experimentally, and the potential risks related to the undesirable properties in the original virus should be carefully examined.

Chapter 3: Development of Manufacturing Process and Quality Assessment

When evaluating the quality of recombinant virus vaccines, in addition to the standard assessments required for conventional vaccines (such as manufacturing process, characterization, specifications and test methods, and stability evaluation), the following points should be taken into consideration.

1. Virus seeds and cells for manufacturing

Procedures for preparing virus seeds and cells for manufacturing (cell banks) should be established by the time of the application for marketing approval. When nonclinical and clinical study results using investigational products, etc. produced before the establishment of the preparation procedures are applied, it is necessary to explain the comparability with the product manufactured after the establishment of the preparation procedures. Note that materials derived from humans or other living organisms (excluding plants) that are used in the production of recombinant virus vaccines, including raw materials used for preparation of virus seeds and cells for manufacturing, must meet the Standards for Biological Materials (MHLW Notification No. 210, 2003).

In the manufacture of recombinant virus vaccines, a seed lot system is commonly used in their preparation procedure. For each of MVS and WVS, appropriate quality control aspects (such as identity, purity [e.g., absence of adventitious infectious agents], and infectivity titers) should be specified based on the properties of the established recombinant virus, and the storage period and renewal methods should be specified taking into account the storage method and the stability during storage. The assessment of the genetic stability of the recombinant virus during the course from the MVS to the final product is critical. Possible occurrence of events such as genetic mutations, reversion of pathogenicity, and change in replication competence at the maximum number of passages expected in manufacturing or at a number exceeding it should be evaluated. For the evaluation of genetic stability, Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products (PMSB/ELD Notification No. 3 issued by the Director of ELD, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare, dated January 6, 1998) (ICH Q5B Guideline) may be helpful.

When a method other than seed lot system is used, how the consistency of quality is ensured should be explained, including the control procedure in the adopted manufacturing system.

For the preparation and characterization of cells for manufacturing, Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products (PMSB/ELD Notification No. 873 issued by the Director of ELD, PMSB, MHW, dated July 14, 2000) (ICH Q5D Guideline) may be helpful.

2. Characterization

As for characterization, in alignment with the characteristics of the recombinant virus, such as replication competence, necessary evaluations should be determined for each characteristic. For aspects covered by Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (PMSB/ELD Notification No. 571 dated May 1, 2001) (ICH Q6B Guideline), characterization regarding the structure, physicochemical properties, biological properties, etc. should be performed with reference to this Guideline in alignment with the characteristics of the recombinant virus.

The characteristics of impurities, etc. in commercial production should be clarified, and the necessity of setting specification tests should be considered. Impurities expected in recombinant virus vaccines include not only those expected in conventional biotechnological products, such as process-related impurities including medium-derived and cell-derived components, but residual fragments of the plasmid used to construct the

virus, incomplete recombinant virus particles that cannot induce the intended immune reaction, and virus particles muted during manufacturing process, such as those that have acquired replication competence after reverse mutation (in case of replication-incompetent recombinant virus vaccines). For mutated viruses occurring during the manufacturing process, the necessity of setting specification tests should be considered.

3. Specification tests and control methods

To ensure the quality and consistency of each lot of a recombinant virus vaccine, specifications and testing methods for the drug substance and drug product should be established based on characterization results, and critical intermediates should be controlled. For investigational products, a provisional specification should be set in consideration of the safety of subjects, taking into account the characteristics of recombinant viruses. When applying for marketing approval, the applicant should explain the rationale for the specification for commercial production, taking into account the results of clinical trials and the latest scientific knowledge.

For the specification tests required for the drug substances and drug products of recombinant virus vaccines, the specification tests (such as potency, identification, and sterility) commonly set for vaccines may be useful as reference. Furthermore, tests required in the Japanese Pharmacopoeia according to the dosage form (such as insoluble particulate matter, and uniformity of dosage units) may also be expected. In addition, depending on the characteristics of the recombinant virus, the necessity of the following control tests should be considered.

(1) Virus level

Specification to control the number of virus particles, amount of virus genome, etc. in the vaccine product

(2) Potency

a. Infectivity titer

Specification to control infective virus load

b. Specific infectivity titer (ratio infectivity titer to virus level)

Specification to control the ratio of infectivity titer to virus level of the vaccine product

c. Transgene expression

Specification to confirm the expression level of the target transgene

(3) Absence of replication-competent viruses

Specification to confirm the absence of replication-competent viruses for replication-

incompetent virus vaccines

(4) Confirmation of replication competence

Specification to confirm that the replication competence has not changed (i.e., is equivalent to that of MVS and WVS) after the manufacturing process for replication-competent recombinant virus vaccines

4. Stability testing

For investigational products, their stability should be ensured for each lot until completion of the vaccination in the clinical trials in which they are planned to be used. For the stability testing to establish final shelf lives for marketing applications, Stability Testing of Biotechnological/Biological Products (PMSB/ELD Notification No. 6 issued by the Director of ELD, PMSB, MHW, dated January 6, 1998) (ICH Q5C Guideline) can be helpful.

Chapter 4: Nonclinical Studies

Nonclinical evaluations should be conducted with reference to Guidelines for Nonclinical Studies of Vaccines for Infectious Disease Prevention (Revised) (PSB/PED Notification No. 0327-1 issued by the Director of PED, PSB, MHLW, dated March 27, 2024); evaluations covered by these Guidelines should be conducted in accordance with them. In addition, the following points should be considered as specific evaluations of recombinant virus vaccines.

1. Selection of animal species/models

Although, for a recombinant virus vaccine under development, animal species appropriate for nonclinical studies are not always available, animal species that are sensitive to the biological effects of the vaccine should be selected.

Specifically, for replication-incompetent virus vaccines, species that demonstrate an immune response to the intended antigen expressed *in vivo* should be selected.

For replication-competent recombinant virus vaccines, species that immunologically respond to the intended antigen expressed from the recombinant virus particles replicated *in vivo* should be selected. When animals in which the recombinant virus can replicate *in vivo* are unavailable, at least an animal species that shows an immune response to the intended antigen expressed *in vivo* should be selected.

When the above-mentioned animal species are not available and there is no choice but selecting another animal species, it is advisable to consult the regulatory agency in advance about the nonclinical study program.

2. Pharmacology (Primary Pharmacodynamics)

For immunogenicity, it may be useful not only to evaluate the intended immune response but also to evaluate immune responses induced *in vivo* against other viral proteins in the recombinant virus.

When interactions between the immunogenicity of a recombinant virus vaccine and another approved vaccine are expected, their impact should be investigated.

3. Nonclinical Safety

Nonclinical safety evaluation of recombinant virus vaccines should be performed in the same manner as that of conventional vaccines.

Note that the nonclinical safety data for recombinant virus vaccines that should be attached to their marketing application must basically be collected and prepared in accordance with the Ministerial Ordinance on Good Laboratory Practice (GLP) for Nonclinical Safety Studies of Drugs (MHW Ordinance No. 21 in 1997).

4. Biodistribution

A thorough understanding of the distribution and persistence characteristics of the recombinant virus in the body is important as basic data for evaluating the efficacy and safety of the recombinant virus vaccine. In principle, biodistribution studies should be conducted prior to the start of the first clinical trial in Japan. By clarifying not only the distribution to the intended biological tissues but also the distribution to non-intended biological tissues, reproductive tissues, etc. from the analysis of biodistribution, it is possible to identify organs to be focused when evaluating the safety in humans and evaluate the risk of unintended integration. When distribution in reproductive tissues, etc. is observed, its disappearance should also be evaluated. Furthermore, the results of biodistribution studies provide information on the distribution and persistence of the recombinant virus in the body, which will be useful for examining the evaluation period for the efficacy and safety in humans. In addition, biodistribution study results may be useful in discussing the toxicological significance of any tissue-specific abnormal findings observed in toxicity studies.

In principle, biodistribution studies should be conducted using the development product. However, when the biodistribution for the development product can be explained based on the results of biodistribution studies, clinical studies, and other studies conducted for other recombinant virus vaccines with the same genes except for the expression construct, the

need for biodistribution studies using the development product may be obviated.

5. Assessment of the risk of germline integration (gene integration assessment)

When biodistribution studies have demonstrated that the recombinant virus is distributed in reproductive tissues, the risk of germline integration should be assessed with reference to ICH Considerations: General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors (2006) (Office Communication of the Office of Counsellor for Medical Devices and Regenerative Medical Products, ELD, PFSB, MHLW, dated June 23, 2015).

6. Assessment of shedding of recombinant viruses

Understanding shedding of the recombinant virus (the risk of transmission via secretion or excreta) provides important information for planning clinical trials. Because clinical trials of recombinant virus vaccines are expected to be conducted in an open environment, shedding of the recombinant virus should be evaluated prior to the start of the first clinical trial in Japan, and based on the evaluation results, a strategy to control the recombinant virus in clinical trials should be determined. When results of other studies such as a biodistribution study of the recombinant virus or relevant information on the original virus are available, shedding of the recombinant virus can be in some cases evaluated even if separate studies to evaluate the shedding are not conducted. For evaluation methods, ICH Considerations: General Principles to Address Virus and Vector Shedding (2009) (Office Communication of the Office of Counsellor for Medical Devices and Regenerative Medical Products, ELD, PFSB, MHLW, dated June 23, 2015) may be helpful.

When shedding is observed for an infectious recombinant virus and transmission to third parties cannot be controlled clinically, possible risks expected when transmission to third parties (including neonates, pregnant women, and immunosuppressed patients) occurs should be assessed.

Chapter 5: Clinical Studies

Clinical studies should be conducted with reference to Guidelines for Clinical Studies of Vaccines for Infectious Disease Prevention (Revised) (PSB/PED Notification No. 0327-4 issued by the Director of PED, PFSB, MHLW, dated March 27, 2024) and Guidance on Clinical Evaluation of Travelers' Vaccines, etc. (PSEHB/ELD Notification No. 0407-1 issued by the Director of ELD, PSEHB, MHLW, dated April 7, 2016); evaluations covered by these Guidelines and Guidance should be conducted in accordance with them. In

particular, when the vaccine is administered to humans for the first time, the study plan should be determined with reference to Guidance on Safety Assurance in First-in-Human Studies in Drug Development (PSEHB/PED Notification No. 1225-1 issued by the Director of PED, PSEHB, MHLW, dated December 25, 2019). In addition, the following points should be considered as evaluations specific to recombinant virus vaccines.

1. Principles for efficacy evaluation

Efficacy of recombinant virus vaccines should be evaluated in the same manner as that of conventional vaccines. However, when evaluating the efficacy of a recombinant virus vaccine consisting of a recombinant virus into which the desired antigen gene has been inserted, attention should be paid to the possibility that in individuals who have antibodies against virus proteins other than the desired antigen, these antibodies may affect the efficacy of the vaccine. Furthermore, it should be noted that past history of administration of a recombinant virus vaccine or an approved vaccine may affect the efficacy of the other vaccine in cases such as where the recombinant virus is neutralized by antibodies induced by administration of the approved vaccine.

2. Principles for safety evaluation

The safety of the recombinant virus vaccine under development should be evaluated with an appropriate observation period determined based on the characteristics of the original virus and the recombinant virus, results of nonclinical studies, results of clinical studies conducted to date, etc.

When the recombinant virus vaccine under development is generated from an original virus by modifying pathogenicity-related genes, etc., to achieve attenuation, as for the adverse events possibly related to the pathogenicity of the original virus, it is important to be ready for performing additional analyses to assess the possible reversion of pathogenicity by isolating virus from subjects and performing genetic analyses, etc., for example, when making diagnosis in subjects who develop symptoms for efficacy evaluations or when strongly suspecting a reversion of the pathogenicity of the recombinant virus in safety evaluations.

Furthermore, when the original virus is known to exhibit a specific cell/tissue tropism or when nonclinical biodistribution studies demonstrate that the recombinant virus distributes to specific organs/tissues, it is important to collect and evaluate adverse events related to these organs/tissues.

The observation period for safety evaluation should be determined taking into account

the time to elimination of the original virus from the human body; the retention periods in animal tissues and shedding period of the recombinant virus demonstrated in nonclinical studies; and the retention periods in the human blood and other tissues/organs and shedding period of the recombinant virus shown in clinical studies. Furthermore, when the recombinant virus for the development vaccine is replication competent, the observation period should be more carefully determined than replication-incompetent cases, taking into account the replication period in the human body. The appropriateness of the observation period should be reviewed based on the safety data accumulated as the clinical program progresses, and the necessity of updates should be considered, as appropriate.

3. Principles for evaluation of shedding and transmission to third parties

Using ICH Considerations: General Principles to Address Virus and Vector Shedding (2009) (Office Communication of the Office of Counsellor for Medical Devices and Regenerative Medical Products, ELD, PFSB, MHLW, dated June 23, 2015) for reference, the risk for the recombinant virus administered to study subjects to be transmitted to third parties other than the vaccinated should be assessed.

When shedding of an infective recombinant virus is expected to occur at the site of administration, or in urine, feces, saliva, etc., there is a risk of transmission of the shed recombinant virus particles to third parties. Therefore, the amount of recombinant virus particles contained in the excreta should be measured over time and the persistence and duration of shedding in the human body should be determined. Quantification of recombinant viruses in blood is necessary for not only understanding the persistence in the human body but also evaluating the risk of transmission to third parties via blood such as in cases of bleeding and blood donation.

If risks of transmission to third parties are shown, the safety risk caused by transmission to third parties should be evaluated, and measures to minimize the risk should be determined. In particular, when the recombinant virus vaccine under development is replication competent and has been demonstrated to shed, measures to prevent transmission of the virus from vaccine recipients to third parties should be determined, since there is a possibility of secondary infection from transmitted third parties.

It should be noted that the effects of shedding of a recombinant virus on the environment must be separately evaluated based on 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) (hereinafter referred to as the Cartagena Act).

4. Necessity and general principles for determining contraception periods

The necessity of contraception and an appropriate duration of contraception should be determined based on the results of studies of the recombinant virus, such as studies on vertical infectivity, nonclinical biodistribution studies, and reproductive and developmental toxicity studies. When women of childbearing potential are included in a clinical trial, information obtained in preceding clinical studies, such as the persistence of the recombinant virus in human blood and the expected time to shedding into body fluids will be helpful.

5. Assessment of the risk of germline integration (gene integration assessment)

When nonclinical biodistribution studies have demonstrated that the recombinant virus is distributed in reproductive tissues, the risk of germline integration should be assessed with reference to ICH Considerations: General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors (2006) (Office Communication of the Office of Counsellor for Medical Devices and Regenerative Medical Products, ELD, PFSB, MHLW, dated June 23, 2015).

Chapter 6: Post-marketing Activities

To ensure that the recombinant virus vaccine is used in compliance with the regulations on type 1 use approved based on the Cartagena Act, necessary measures should be taken, such as an electronic package insert and publicizing the regulations for materials.

End