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Excerpt from Integrated Report "Research for Quality/Safety Evaluation in Development of Live Recombinant Vaccines Expressing Heterologous Antigens"

Considerations on Development of Recombinant Virus Vaccines for Prevention of Infections

1. Introduction

Advancement of genetic engineering technology and biotechnology has enabled development of vaccines for prevention of infections of which manufacture was deemed difficult with traditional techniques. For example, a reverse genetics approach, one of the techniques using genetic engineering technology, has accelerated generation of recombinant viruses. In addition, vaccines designed to express target genes such as those using virus vectors, which are originally used for gene therapy, are being developed. The vaccines for prevention of infections developed using recombinant viruses (hereinafter referred to as "recombinant virus vaccines") differ from traditional ones in the active substance or actual inoculants; the former are viruses with the target genes integrated, while the latter are antigen proteins or virus particles. Because the actual inoculants are viruses, the recombinant virus vaccines stimulate the immune system through mechanisms similar to those occurring in the event of virus infection, being capable of continuously stimulating both humoral immunity and cellular immunity, and thus are expected to induce a more potent immune response than traditional vaccines. In particular, efforts to develop recombinant virus vaccines against pathogens such as Ebola virus and human immunodeficiency virus (HIV) that potentially threaten public health but have no approved effective vaccines are being made, and their practical application is expected. In addition, in some countries outside Japan, recombinant virus vaccines against dengue virus and Japanese encephalitis virus have already been approved. The recombinant virus vaccines being developed are expected to have high efficacy, but they may have safety in newborns, pregnant women, and immunocompromised patients that are greatly different from that of traditional vaccines. In particular, replication competent recombinant virus vaccines may have an increased risk of transmission to third parties and thus must be carefully evaluated for a safety risk associated with virus shedding. For these characteristics, recombinant virus vaccines should undergo quality, non-clinical, and clinical evaluation different from those for traditional vaccines, and should be implemented with additional measures to ensure safety.

This guidance supplements "Guideline for Clinical Studies of Vaccines for Prevention of Infections" and "Guideline for Non-Clinical Evaluation of Vaccines for Prevention of Infections" and presents points to note for quality, non-clinical, and clinical evaluation specific to development of recombinant virus vaccines.

2. Objectives

This guidance organizes principles and points to note in quality, non-clinical, and clinical evaluation for development of recombinant virus vaccines, aiming to identify new perspectives in ensuring safety and evaluating efficacy. It should be noted that the content reflects discussions based on scientific knowledge at the present time and thus is subject to change in response to scientific progress in the future.

* This English version is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

3. Scope of application

This guidance applies to recombinant virus vaccines for prevention of infections prepared using the following genetic engineering designs.

- Vaccines containing the active substances of viruses that have altered antigenicity, pathogenicity, or replication competence by integrating exogenous genes using genetic engineering technology (hereinafter, referred to as "recombinant viruses").
- Vaccines containing the active substances of recombinant viruses that are designed to acquire antigenicity after inoculation by expressing the target antigen in the body of vaccine recipients

The scope of application of this guideline includes vaccines containing viruses with genes involved in viral replication (hereinafter, referred to as "replication competent virus vaccines") and vaccines containing viruses without them (hereinafter, referred to as "replication incompetent virus vaccines").

On the other hand, this guidance does not apply to vaccines containing the active substances of chemically inactivated recombinant viruses using formalin, etc. In addition, it does not apply to vaccines containing the active substances of recombinant viruses that are manufactured using genetic engineering technology but deemed to have the genomic composition equivalent to that of naturally occurring viruses (natural occurrence) or ones containing the active substances of nucleic acids such as gene expression constructs and mRNA either. However, some of the principles may be applicable, and consultation with PMDA is encouraged where appropriate.

4. Principles for development

At the present time, no recombinant virus vaccines have been approved in Japan, and a large part of the safety and efficacy evaluation approaches are not covered by traditional guidelines or notifications. In addition, because vaccines for prevention of infections are supposed to be inoculated in an indefinite number of healthy people for prophylactic purposes, safety of recombinant virus vaccines should be adequately evaluated for any risk that is potentially posed by them but not found in traditional vaccines to ensure appropriate development. Eligible infections to be prevented by recombinant virus vaccines are assumed to be ones that must be prevented by vaccines for public health purposes and have a need and characteristics justifying development of recombinant virus vaccines but not traditional inactivated vaccines or live vaccines.

5. Points to note for quality evaluation and characterization

Quality evaluation of recombinant virus vaccines should include the following studies. The information on the following points is required according to the development stage because it constitutes an important part of non-clinical and clinical study design formulation and assessment for potential risks of recombinant virus vaccines.

(1) Viruses used as the source of recombinant viruses

Information on characteristics of a pre-recombination or wild-type virus used as the source of a recombinant virus is important in evaluating characteristics of the recombinant virus. Usually, a recombinant virus is constructed by altering specific characteristics of the pre-recombination virus. To evaluate alterations in characteristics (e.g., infectivity, tropism toward specific cells/tissues) of the recombinant virus, information on characteristics of the pre-recombination virus should be adequately collected.

Because recombinant virus vaccines are generally intended to be used for prevention of infections in healthy people, viruses harboring genes potentially integrated into chromosomes of the vaccine recipient are not accepted as pre-recombination ones in principle.

(2) Characterization of recombinant viruses

The recombinant virus should be explained in terms of its construction method and characterized through the following evaluations or analyses. Depending on characteristics of the recombinant virus, additional studies may be required.

- Gene sequencing (genes related to replication, target genes, genes related to their expression as well as flanking regions of the concerned genes)
- Species specificity, tropism toward specific cells/tissues, replication attribute, and cytotoxicity as well as comparisons with the pre-recombination virus in terms of these characteristics
- Check of amount of antigen expressed, expression efficacy, and persistence in infected cells
- Assessment for recombination and reassortment risks between recombinant and wild-type viruses
- Assessment of a risk of chromosomal integration
- Evaluation of the process-related impurities specific to recombinant viruses (e.g., residual plasmids, residual helper viruses)

(3) Evaluation in the manufacturing process

Infectivity titer per virus particle in the vaccine product is useful in evaluating consistent production of recombinant viruses and thus should be measured. In addition, recombinant viruses should be evaluated for genetic stability (mutation, reversion of pathogenicity, changes in replication competence) in the manufacturing process. Recombinant viruses in the vaccine product are also encouraged to be evaluated for genetic heterogeneity that would indicate consistency of the manufacturing method.

6. Points to note for non-clinical evaluation

Non-clinical evaluation of recombinant virus vaccines is basically required to comply with the “Guideline for Non-Clinical Evaluation of Vaccines for Prevention of Infections” where applicable, but points provided below are specific to recombinant virus vaccines and thus should be included in the evaluation.

(1) Selection of animal species/models

Even if a pre-recombination virus used as the source of the recombinant virus is not practically infectious to non-human animals, the recombinant virus inoculated in animals may express antigens in the cells. With

such a case taken into account, animal species appropriate for non-clinical evaluation should be selected. In addition, studies using recombinant viruses may require testing facilities at Biosafety Level 2 (BSL2), potentially precluding them from being conducted in compliance with the Good Laboratory Practice (GLP). Even in such cases, the studies are encouraged to be conducted in accordance with the GLP wherever possible.

(2) Biodistribution studies

To understand characteristics of the recombinant virus and obtain base data for the safety and efficacy evaluation, biodistribution studies should be conducted before the start of a phase I study. An analysis on biodistribution data may show the distribution in not only the target tissues but also unintended tissues and germ-line cells in the body, allowing the applicant to identify organs of interest in evaluating safety in humans and a risk of unintended integration. Thus, the biodistribution data can be useful in discussing toxicological meanings of tissue-specific abnormal findings detected in toxicity studies. If biodistribution studies raise concerns, conduct of additional non-clinical studies should be considered. An investigation of persistence of the recombinant virus including the distribution and elimination would deliver information that may help determine an appropriate evaluation period in clinical studies. The information obtained should be reflected in clinical study design.

(3) Evaluation of risk of integration into germ-line cells

If biodistribution studies show that the recombinant virus is distributed in reproductive tissues, evaluation should be performed with reference to the "ICH Considerations 'General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors'" (Administrative Notice dated June 23, 2015).

(4) Evaluation of shedding of recombinant viruses

In principle, shedding of recombinant viruses should be evaluated. Shedding of recombinant viruses can be evaluated in toxicity studies for other purposes. For the evaluation method, the "ICH Considerations 'General Principles to Address Virus and Vector Shedding'" (Administrative Notice dated June 23, 2015) should be referred to.

(5) Genotoxicity and carcinogenicity studies

Usually, vaccines do not require genotoxicity or carcinogenicity studies. However, if characteristics of the pre-recombination or recombinant virus raise concerns, genotoxicity and carcinogenicity should be evaluated, and where appropriate, conduct of studies in a feasible and appropriate manner should be considered.

(6) Evaluation of immunogenicity

Evaluation of immunogenicity should cover not only immune responses specific to the target antigen but also biologically induced immune responses to the recombinant virus itself and the other virus proteins contained in it.

If a recombinant virus vaccine is prepared using an approved live vaccine as the pre-recombination virus, non-clinical studies to evaluate interference of either approved live vaccine or test recombinant vaccine with immunogenicity of the other should be conducted by inoculating the test recombinant vaccine after inoculation of the approved live vaccine or vice versa.

(7) Study with inoculation in immunocompromised animals

Replication competent recombinant virus vaccines may cause serious symptoms in newborns, pregnant women, and immunocompromised patients under circumstances where they do not cause any pathological conditions in healthy people. To evaluate such a possibility, studies with inoculation in immunocompromised animals should be conducted.

7. Points to note for clinical evaluation

(1) Principles for evaluation on shedding and transmission to third parties

Recombinant virus vaccines have an ability to express the target genes in the human body and present the antigen. If recombinant virus shedding from vaccine recipients are transmitted to newborns, pregnant women, and immunocompromised patients, serious toxicity may occur. Even non-replication competent recombinant virus vaccines should be subjected to evaluation to confirm that they do not replicate in the human body and are unlikely to be transmitted to newborns, pregnant women, and immunocompromised patients. On the other hand, replication competent recombinant virus vaccines are supposed to have an increased risk of transmission to newborns, pregnant women, and immunocompromised patients. For such increased risk, virus shedding should be carefully evaluated.

In clinical evaluation usually starting with phase I studies, amounts of recombinant viruses at least in the inoculation site, blood, and body fluids where the viruses are supposed to be shed should be measured over time using evaluable specimens to capture persistence and duration of shedding in the human body. Information on the persistence and duration of shedding in the human body can be used as supporting data to establish preventive measures against transmission from vaccine recipients to third parties in subsequent clinical studies.

Omission of preventive measures against transmission from vaccine recipients to third parties, if any, should be justified. In addition, information on transmission from vaccine recipients to close contacts should be collected as well. For recombinant viruses that are not shed and are rapidly eliminated from blood, monitoring of close contacts for any signs of infection may suffice. For vaccines containing replication competent recombinant viruses that are persistently shed, on the other hand, it should be noted that examinations to rule out infections in close contacts are continuously required.

(2) Principles for contraception period

In clinical studies, a contraception period for males should be appropriately specified based on data in biodistribution studies and shedding of recombinant viruses. For women of childbearing potential, on the other hand, a contraception period should be specified based on data not only in non-clinical studies but also on persistence of recombinant viruses in human blood and duration of shedding into body fluids where the viruses are supposed to be shed.

(3) Principles for safety evaluation

Safety of recombinant virus vaccines should be evaluated with focus on the following risks. These risks should be carefully investigated in clinical studies at early stages.

- For non-replication competent recombinant virus vaccines, a risk of unexpected replication of the recombinant virus in vaccine recipients' bodies.
- Risks of accidental recombination with genes of the other pathogenic viruses and adverse events owing to recombinant variants in vaccine recipients
- A risk of adverse events in specific tissues and organs for the viruses that are shown to be distributed in these tissues and organs in biodistribution studies, including a relationship between the events and distribution

(4) Principles for immunogenicity evaluation

Humoral or cellular immunity responses induced by a recombinant virus vaccine should be investigated to the extent possible at early stages of the clinical development. The extent of investigation can be determined based on results in non-clinical studies and existing information on the pre-recombination virus.

For vaccines using viruses of an approved live vaccine as pre-recombination viruses, interference of either approved live vaccine or recombinant vaccine with immunogenicity of the other, provided in 6. (6), should be evaluated in clinical studies as well in view of inoculation schedule of the approved live vaccines in clinical practice.

(5) Principles for efficacy evaluation

For recombinant virus vaccines, a risk of adverse events in not only vaccine recipients but also third parties cannot be ruled out. From a risk-benefit viewpoint, clinical studies are required to demonstrate adequate efficacy using prevention against onset of symptoms or infection as the efficacy endpoint.

8. Post-marketing investigations

The risk management plan should cover transmission to third parties provided in 7. (1) and safety evaluation in 7. (3) to continue collecting information.

9. Other points to note

If inoculation schedule using a recombinant virus vaccine for the primary series and an inactivated vaccine for the booster dose is assumed, consultation with PMDA regarding the development strategy should be made.

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