**(Attachment)**

# Questions and Answers (Q & A) on Guidelines for the Development of Recombinant Virus Vaccines for Infectious Disease Prevention

## Chapter 1, "3. Scope"

(Q1) Please provide specific examples of recombinant viruses that are intended to be within the scope of these Guidelines.

A1

For example, recombinant viruses such as a replication-incompetent recombinant adenovirus with the insertion of a part of a different virus' genome, a replication-competent recombinant vesicular stomatitis virus with modification of genes while maintaining replication ability, and a recombinant dengue virus with the insertion of a genome derived from a different serotype of the same virus are intended to be within the scope.

(Q2) The Guidelines state that "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." Please provide specific examples that show what kinds of viruses are not within the scope of these Guidelines.

A2

Genetically engineered viruses that are considered outside the scope of Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms) (Act No. 97 of 2003) (the so-called Cartagena Act) are intended. If you wish to confirm whether a recombinant virus of interest is considered a natural occurrence (*), you are advised to utilize Cartagena Act-related consultation services.

* "Natural occurrence" means an organism that contains nucleic acid, or a replicated product thereof, obtained through use of the technology described in Article 2, Item 2 of the Enforcement Regulations of the Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Ministry of Finance, Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labour and Welfare, Ministry of Agriculture, Forestry and Fisheries, Ministry of Economy, Trade and Industry, and Ministry of the Environment Ordinance No. 1 of 2003).

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

(Q3) The Guidelines state that "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 considering '1. History of the development of recombinant virus' and '2. Properties of recombinant virus' below." Please provide examples that show what descriptions are required for trial-related documents such as the Investigator's Brochure.

A3

A party who intends to sponsor a clinical trial or a party who intends to conduct a clinical trial on their own initiative is required to provide information that supports the proper conduct of the clinical trial to the investigators, etc. The party is asked to appropriately provide the information in various kinds of documents, such as the Investigator's Brochure, in which the quality and other aspects of the test article should be described; the Protocol, in which the handling and other aspects of the test article should be described; and other documents such as a document that describes the reason that the trial is considered scientifically justifiable, in which basic information on the recombinant virus that is related to the efficacy and safety of the vaccine, information that supports the actions required in case of accidental leakage, etc. should be described. The basis for the information should be explained by describing an outline of the study results concerning "1. History of the development of recombinant virus" and "2. Properties of recombinant virus" or by citing the literature.

**Chapter 2, "2. Properties of recombinant virus"**

(Q4) Regarding "(2) Physicochemical properties of recombinant virus, 1) Stability assuming accidental leakage, etc.," please provide specific examples that show what assessments should be performed.

A4

To consider appropriate actions to take when accidental leakage occurs in the environment expected during shipment or use, such as when vials of a recombinant virus vaccine are broken or when vaccine solution is leaked during use, for example, studies to explore the stability of recombinant viruses, as measured by the infectivity or replication competence of the recombinant virus, assuming that recombinant virus particles are attached to the surface of a

plastic object, a cotton cloth, a metal object, etc. are expected. Information obtained from such studies may be useful in evaluating the risk of unintended transmission to humans and others.

**Chapter 2, "2. Properties of recombinant virus, (3) Biological properties of recombinant virus, 6) Possibility of emergence of mutant viruses"**

(Q5) The Guidelines state in "6) Possibility of emergence of mutant viruses" that: "Whether the original virus likely undergoes homologous recombination or genetic reassortment (hereinafter referred to as "homologous recombination, etc.") with other viruses should be explained using the 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." Please provide examples that show what kind of evaluation is supposed to be performed.

A5

When events of homologous recombination, etc. of the original virus with allogeneic viruses have been reported, they should be explained using the literature, etc.

The possibility that the recombinant virus undergoes homologous recombination, etc. with wild-type viruses should be explained taking into account the following points.

- Characteristics of the recombinant virus genome (such as sequences or genome segments that are likely to cause homologous recombination, etc.). In addition, when the virus genome has been modified to reduce the risk of homologous recombination, etc., the measures in the genome design for reducing the risk by modifying a gene sequence.
- The relationship between the biodistribution data of the recombinant virus and the expected infection sites of the wild-type virus.
- The dosage of the recombinant virus vaccine

When the risk of homologous recombination, etc. cannot be neglected, risks associated with homologous recombination, etc. between the recombinant virus and the wild-type virus should be explained.

**Chapter 4, "2. Pharmacology (primary pharmacodynamics)"**

(Q6) The Guidelines state that "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 than the antigens." Please provide examples that show regarding what information the evaluations should be conducted.

A6

When specific genes have been inserted for modification of characteristics, such as replication competence or tissue tropism, the effects of the immune response to the proteins expressed by these genes should be evaluated. Furthermore, it may also be useful to evaluate the impact of unintended immune reactions against the structural proteins of viral vectors or viral proteins other than the desired antigen proteins.

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| (Q7) The Guidelines state that "When interactions between the immunogenicity of a recombinant virus vaccine and another approved vaccine are expected, their impact should be investigated." Please provide examples of situations where the investigation is necessary. |

A7

For example, when the active ingredient of any of the approved vaccines such as measles vaccine, varicella vaccine, and smallpox vaccine is allogeneic to the original virus for the recombinant virus vaccine under development or the virus from which a desired gene is derived, the immunity acquired from the vaccine administered earlier may prevent or boost the immunity expected from the vaccine administered later. When such an effect is expected, its impact may need to be evaluated in nonclinical or clinical studies.

**Chapter 4, "3. Nonclinical safety"**

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| (Q8) For a recombinant viral vaccine under development, when it is difficult to follow Ministerial Ordinance on Good Laboratory Practice for Nonclinical Safety Studies of Drugs (MHLW Ordinance No. 21 of 1997) (hereinafter referred to as "GLP"), how should the developer respond? |

A8

In principle, any nonclinical safety study is required to be conducted in accordance with Ministerial Ordinance on Good Laboratory Practice for Nonclinical Safety Studies of Drugs (GLP). When nonclinical safety studies cannot be conducted in accordance with GLP because of, for example, the conditions required for experiment sites that use recombinant organisms, the developer is required to clarify the parts that cannot be conducted in accordance with GLP and explain the impact on the safety evaluation.

**Chapter 4, "4. Biodistribution"**

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| (Q9) Do biodistribution studies need to be conducted as GLP studies? |

A9

Data on biodistribution studies are not subject to the GLP requirements, but should be collected and prepared so that reliability is ensured.

(Q10) Please provide specific examples of tissues/organs to be evaluated in biodistribution studies.

A10

In biodistribution studies, evaluation of blood, injection site, draining lymph nodes, gonads, adrenals, brain, spinal cord (cervical, thoracic, lumbar), liver, kidneys, lungs, heart, and spleen should generally be considered. In addition, whether additional tissues/organs need to be evaluated should be considered, taking into account factors such as the cell/tissue tropism of the recombinant virus, the action of expressed proteins, the characteristics of the recombinant virus vaccine, and the route of administration.

**Chapter 4, Others**

(Q11) When the characteristics, pharmacokinetics, nonclinical safety, etc. of the recombinant virus for the development product can be explained based on the study results, etc. already obtained in the development of other products generated using the same technology as the development product, is it possible to do away with nonclinical studies that use the development product?

A11

Since it is necessary to make a decision based on the characteristics of individual recombinant viruses, it is advisable to consult the Pharmaceuticals and Medical Devices Agency about a specific development plan, including an explanation of the study results obtained with other products and the appropriateness of doing away with non-clinical studies of the development product.

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