(Attachment)

Questions and Answers (Q & A) on Guidelines for Nonclinical Studies of Vaccines for Infectious Disease Prevention

1.3. Scope

Question 1　Regarding "1.3. Scope": If other guidelines have been issued individually for various vaccines, will they be prioritized over the present Guidelines?

(Answer)

If similar aspects are discussed in both the guidelines for individual vaccines and the present Guidelines and there is a difference in the descriptions, the guidelines for individual vaccines will take precedence. On the other hand, guidelines for individual vaccines may not cover all general aspects of vaccine development. In such cases, refer to the present Guidelines.

2. General Principles

Question 2　The Guidelines state in "2. General Concepts" that "However, when there is a scientifically justifiable reason, nonclinical studies required for other novel vaccines are not always required, such as when a novel vaccine is a combined vaccine consisting only of active vaccine ingredients already approved in Japan or when the composition and pharmacological effects of a novel vaccine are similar to those of an approved vaccine for which there are many clinical use results and its safety has been established."

a. Do the "clinical use results" include overseas results?
b. Regarding "active vaccine ingredients already approved in Japan", is it possible to consider whether nonclinical studies can be waived based on existing data for other vaccines manufactured using the same platform, such as in the development of vaccines against variant strains?

(Answer)

a. Yes, they do.
b. A waiver of nonclinical studies may be considered on the basis of individual cases. It is therefore advisable to consult the regulatory authority at an early stage of development.

2.1. Study Design

Question 3　The Guidelines state that "Necessity of nonclinical studies, study type, animal species selection, and study design should be considered based on scientific evidence and the specific characteristics of each vaccine." Is it possible to consider whether nonclinical studies are needed?

(Answer)

As described in the Guidelines, it is possible to consider whether individual nonclinical studies are needed. For example, when a vaccine is developed for an additional indication within the approved dosage range, it may be acceptable to omit nonclinical safety studies.

2.2. Selection of animal species/models

Question 4 Regarding animal species, the Guidelines state that "When selecting animal species for nonclinical studies of a vaccine, usually at least one species that exhibits an immune response to the active ingredient of the vaccine should be used." Regarding this statement:

a. Is it needed to confirm that the animal species presents an immune response to all antigens when selecting an animal species for nonclinical studies of a combined vaccine containing multiple antigens? Or, when a vaccine contains multiple antigens, is it acceptable if an immune response cannot be confirmed for some of the antigens?
b. Is it possible to explain the appropriateness of the selection of animal species using information in published articles and/or results from non-GLP nonclinical studies?

(Answer)

a. It is not necessarily needed to confirm an immune response to all antigens in one species. However, when an immune response can be confirmed only for some antigens in one animal species, it is usually needed to evaluate the vaccine in multiple nonclinical animal species as much as possible so that the efficacy and safety of all antigens become accountable.
b. Yes, it is.

2.3. Test article

Question 5 The Guidelines state that "The test article used in nonclinical studies of a vaccine should appropriately reflect the characteristics (such as composition, dosage form, and manufacturing method) that may affect the efficacy and safety of the product for clinical use." Is it required to conduct additional nonclinical studies if a drug product manufactured with partial changes in the composition, dosage form, and/or manufacturing method of the test article used in nonclinical studies is used in clinical studies?

(Answer)

It is not required to conduct additional nonclinical studies using the post-change drug product, if consistency or comparability can be explained before and after the change in the composition, dosage form, manufacturing method, etc. based on the quality data of the test article used in nonclinical studies and the drug product used in clinical studies. The ICH Q5E Guideline may be helpful for the principles on the evaluations before and after changes. See also Question 20 for formulation changes.

3.3. Safety Pharmacology

Question 6 The Guidelines state that "effects on major physiological functions (central nervous system, respiratory system, and cardiovascular system) can be assessed in nonclinical toxicity studies through the observations and tests in those studies." Is it possible to consider that these effects can be assessed through the general clinical observations and histopathological examinations that are routinely performed in repeated-dose toxicity studies (what are described in Section 5.2)? Or will additional examinations such as FOB, blood gas measurement, blood pressure measurement, and neurobehavioral examination, which are not routinely performed, be required? In addition, is it possible to assess the effects, including those on the cardiovascular system, in repeated-dose toxicity studies in mice or rats?

(Answer)

Effects of a vaccine on major physiological functions (central nervous system, respiratory system, and cardiovascular system) can be usually assessed by the observations and examinations (clinical observations and histopathological examinations) performed in repeated-dose toxicity studies. If immune responses to the vaccine are observed in mice or rats, it is possible to evaluate effects on the major physiological functions using one of these species. It should be noted that a separate safety pharmacology study will have to be considered if, in those assessments, findings of potential safety concerns are observed in repeat-dose toxicity studies and/or clinical studies.

4. Pharmacokinetics

Question 7 The Guidelines state that "for vaccines containing expression plasmid DNA as an active ingredient, biodistribution must be, in principle, investigated before starting clinical studies."

a. What does "in principle" mean? Is it possible to eliminate the need for investigating biodistribution by using knowledge of other products that use the same platform technology (e.g., the same vector)?
b. What methods are acceptable for biodistribution studies? For example, are data from *in vivo* imaging studies acceptable?

(Answer)

a. Biodistribution studies conducted using the development product can be waived if the biodistribution for the development product can be explained based on the results from biodistribution studies that have already been conducted for other products that use the same DNA plasmid vector as that for the development product. It is recommended to consult the regulatory authority at an early stage of the development because it will be necessary to ascertain the differences in quality characteristics between the developed product and other products and whether they affect the biodistribution.
b. They may include PCR and imaging techniques. Regardless of the method used, it is

important to justify the appropriateness of the selected study method.

Question 8 The Guidelines state that "For novel live attenuated vaccines, investigation of shedding is helpful in designing clinical shedding studies." Even if sufficient knowledge for the shedding of the wild type virus is available, should a separate nonclinical shedding study be conducted for a novel live attenuated vaccine with a tissue distribution possibly different from that of the wild type virus, or is conducting the necessary assessments as part of other toxicity studies acceptable?

(Answer)

No separate study needs to be conducted, provided that the shedding of the development product can be explained from information, such as knowledge on the wild-type virus, results from other nonclinical studies, and other findings on shedding.

Even when sufficient knowledge has been obtained about the shedding of the wild-type virus, investigation of the shedding of the novel live attenuated vaccine is necessary if the tissue distribution of the live attenuated vaccine can be different from that of the wild-type virus; however, if shedding of the new live attenuated vaccine can be explained by results from other nonclinical studies, it is not always necessary to conduct a separate study.

5.1. Single-Dose Toxicity

Question 9 When evaluating acute toxicity as part of a repeated-dose toxicity study, is it necessary to perform euthanasia and autopsy after the initial dose only for the purpose of evaluating acute toxicity?

(Answer)

No euthanasia or necropsy after the first dose in a repeat-dose toxicity study is required only for the purpose of evaluating acute toxicity. However, if death or any serious toxicity is observed in a repeated dose toxicity study, necropsy is required to estimate the relationship to treatment.

5.2. Repeat-Dose Toxicity

Question 10 In repeated-dose toxicity studies:

a. Is it acceptable to divide a dose into multiple administration sites?
b. Is it possible to evaluate local tolerance if the dose is divided into multiple administration sites? Is it necessary to conduct a separate local tolerance study in which a single dose is administered to one site?

(Answer)

a. It is acceptable, if there is a reasonable cause that prevents a single clinical dose from being administered to one site in an animal from the perspective of the maximum tolerable dose

that can be administered or animal welfare, etc.

b. If there is a rational reason for administering in divided doses, it is possible to evaluate the local tolerance at the administration sites for the divided doses in the toxicity study.

Question 11 When the intended vaccination interval in clinical use is set to a wide period (e.g., 3 to 7 weeks), how should the dosing interval for nonclinical safety studies be set?

(Answer)

Taking into account the immune response in the nonclinical safety species, a shorter dosing interval (e.g., 2 to 3 weeks) than the clinical dosing interval can be used.

Question 12 The Guidelines state that "If any adverse change is observed in these tests, the reversibility of the change should be examined." How long should the observation period be to adequately assess the recovery?

(Answer)

To evaluate the reversibility of adverse effects, Questions and Answers (Q & A) on the Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (Office Communication of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated August 16, 2012) may be helpful. When a recovery group is included or a recovery study is conducted, it is necessary to determine a study period that is considered to allow for evaluation of recovery or recovery tendency on a case-by-case basis, taking into account the seriousness of adverse changes related to the vaccination and findings from other vaccines.

Question 13 Is it acceptable to consider that repeated-dose toxicity studies are not necessary for vaccines that are intended for single use? Or, is it necessary to assess repeated dose toxicity at +1 dose as an overload condition? If necessary, how should the dosing interval be determined?

(Answer)

Conducting repeated-dose toxicity studies is not mandatory for vaccines administered as a single dose in clinical use. However, it is recommended to conduct repeat-dose toxicity studies given the possibility of change to multiple doses, which could prevent extra toxicity studies in future just in case clinical studies show that additional doses should be considered in clinical use. For dosing intervals, see Question 11.

5.3. Reproductive and Developmental Toxicity

Question 14 The Guidelines mention two kinds of studies in the statement "The need for studies on embryo-fetal development and studies on pre- and postnatal development, including maternal function should be determined based on the intended vaccine recipients in clinical use." Is it possible to evaluate the effects in a single study that includes endpoints for reproduction stages C to E?

(Answer)

Yes, it is.

Question 15 The Guidelines state that "On the other hand, if there is any concern about reproductive and developmental toxicity, this evaluation should be conducted by the time of initiating large-scale clinical trials." What is the criterion for these large-scale clinical trials?

(Answer)

They usually refer to clinical trials in which many women of childbearing potential participate, such as phase III studies.

5.6. Local Tolerance

Question 16 Regarding cumulative irritancy, is it possible to eliminate the need for evaluating cumulative irritancy in nonclinical studies by implementing measures such as avoiding repeated injections at the same site during administration in humans?

(Answer)

Yes, it is.

6.1. Adjuvants

Question 17 What is the definition of a novel adjuvant?

(Answer)

In Guidelines for Nonclinical Studies of Vaccines for Infectious Disease Prevention, a novel adjuvant is defined as an adjuvant that is different from those contained in already-approved vaccines in the constituent, composition ratio, route of administration, etc.

Question 18 Regarding vaccines containing novel adjuvants:

a. The Guidelines state in "3.3. Safety Pharmacology" that "effects on major physiological functions (central nervous system, respiratory system, and cardiovascular system) can be assessed in nonclinical toxicity studies through the observations and tests in those studies." Does this apply to vaccines with novel adjuvants?
b. The Guidelines state that usually, one animal species is to be used in repeated dose toxicity studies and reproductive and developmental toxicity studies. Does this apply to vaccines with novel adjuvants?
c. The Guidelines state that "When a novel adjuvant is used for a vaccine product, the safety of the adjuvant should be evaluated in studies that use the vaccine product, etc. ..." In what cases is the need for the safety evaluation in animals treated with the novel adjuvant alone obviated?
d. When it is necessary to evaluate the adjuvant in animals treated with the novel adjuvant alone, is it acceptable to include a group of animals treated with the novel adjuvant alone in a study of a vaccine product that contains both the new adjuvant and the antigen?

(Answer)

a. Yes, it does.
b. Usually, use of a single species is acceptable, but if systemic exposure to a novel adjuvant has resulted in treatment-related findings in organs and tissues other than the vaccination site and safety concerns are suspected, nonclinical safety studies in 2 species (rodent and non-rodent) should be considered.
c. Evaluating the safety of a novel adjuvant alone is not necessarily required if it can be explained that there is no concern about the safety of the entire vaccine preparation, including for the immune response enhancement reaction caused by the adjuvant.
d. Yes, it is.

Question 19 In relation to pharmacokinetic studies, the Guidelines state that "when a vaccine product contains a novel adjuvant, a biodistribution study for the novel adjuvant may be needed." In what cases will the study be needed? Which substance should be used in the biodistribution study, the adjuvant alone or the vaccine product with the adjuvant?

(Answer)

The necessity of a biodistribution study should be considered from the following pharmacological and toxicological viewpoints. It is generally recommended that the study be conducted using the vaccine product if the biodistribution of the adjuvant can be altered as a result of interactions between the active ingredient and the adjuvant.

[Pharmacological viewpoint]

The effect of an adjuvant is to enhance the immune response to a vaccine. Since the mechanism of action differs depending on the type of adjuvant, when a novel vaccine is developed by using a novel adjuvant, it is necessary to examine the mechanism of action of the adjuvant.

If the adjuvant acts on immune cells at the vaccination site, the need for obtaining information on pharmacokinetics (biodistribution) may be low. On the other hand, for example, if the adjuvant affects cells/tissues other than the vaccination site, information on pharmacokinetics (biodistribution) may be necessary to account for the mechanism of action of the adjuvant.

[Toxicological viewpoint]

The safety evaluation of a novel adjuvant should include not only the assessment of the vaccination site but the effects of systemic exposure. In the safety evaluation, if no concern about the systemic safety of the novel adjuvant in humans was raised based on available information, such as the results of toxicity studies of the vaccine product and the novel adjuvant alone, then the need to obtain information on pharmacokinetics (biodistribution) of the adjuvant may be low. On the other hand, if the systemic safety of the novel adjuvant in humans cannot be explained, information on the pharmacokinetics (biodistribution) of the new adjuvant will be required to interpret the results of the toxicity studies that use the vaccine product.

6.2. Excipients (excluding adjuvants)

Question 20 What assessments are required when a formulation change is made to add excipients other than adjuvants in the development of a vaccine product? Is it necessary to conduct nonclinical studies for the vaccine product after the formulation change?

(Answer)

It is not necessary to conduct nonclinical studies of the vaccine product after the formulation change if it can be explained that there is no potential impact on the efficacy and safety of the vaccine product based on data concerning the added excipients and assessment results concerning the quality attributes of the vaccine product before and after the formulation change.

End