(Attachment)

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

3. Considerations for Clinical Development

Question 1 What kind of investigation is required in clinical studies when a novel adjuvant is developed?

(Answer)

Dose finding studies should be conducted to ensure that the appropriateness of the product formulation (the level and ratio of the adjuvant and active ingredient) can be demonstrated by evaluating multiple combinations of adjuvant and active ingredient levels.

3.1.1. Phase I studies

Question 2 The Guidelines state that "the conduct of phase I studies in Japanese healthy adults may not be required in cases such as where appropriate overseas clinical study data are available in the development of a vaccine for specific populations such as children and the elderly." What data specifically do the overseas clinical study data intended here refer to?

(Answer)

In the development of vaccines for specific populations such as children, for example, if necessary information (such as tolerability and initial investigation of dosages) has been obtained from overseas phase I studies in healthy adults, it may not be required to conduct Japanese phase I studies in healthy adults. It is advisable to consult with PMDA as it must be decided on a case-by-case basis.

3.1.2. Phase II studies

Question 3 The Guidelines state that if a Japanese phase II study is conducted with reference to a dosage established overseas, it is required to explain that the proposed dosage is appropriate for the Japanese population. In what situations does the dosage in the Japanese have to be reconsidered in the development of vaccines?

(Answer)

For example, the dosage for the Japanese needs to be reconsidered in the following cases:

* Cases where referring to overseas clinical study results is clearly unreasonable, such as when antibody titers in Japanese individuals are markedly lower (or higher) compared to those observed in preceding overseas clinical studies.
* Cases where the target population (e.g., age) and dosing schedule in Japan are significantly different from those in other countries and it is difficult to develop the vaccine with the same dosing schedule as in those countries.

In general, it is advisable to start consultations with PMDA from the early stages of development and to deepen mutual understanding of the availability of overseas clinical study results for the target product.

3.1.4. Post-marketing activities

> Question 4 In post-marketing surveillance or other studies, is it possible to perform the "1. Investigation of the effectiveness in special risk groups (such as the elderly, immunocompromised patients, and patients with specific diseases)" using an epidemiological research method (such as a vaccine effectiveness study with a test-negative design)?

(Answer)

Epidemiological research methods can be used for post-marketing surveys/studies. Appropriate methods should be chosen considering the characteristics and limitations of each method.

> Question 5 The Guidelines state that one of the purposes of the post-marketing surveys/studies is to perform "2. Long-term assessment of endpoints such as the persistence of vaccine effectiveness". However, it may be unfeasible to conduct a randomized, double-blind, placebo-controlled study on a large scale as a post-marketing effectiveness survey/study. Is it acceptable to conduct a long-term investigation using an immunogenic endpoint as an effectiveness measure of a vaccine?

(Answer)

Yes, it is.

3.4. Special Discussions on Clinical Studies of Combined Vaccines

> Question 6 Regarding efficacy evaluation of combined vaccines, the Guidelines state that a combined vaccine should, in principle, be compared against a control group receiving simultaneous administration of the individual vaccines comprising the combined vaccine. Is simultaneous administration required when multiple vaccines with different dosing schedules are administered?

(Answer)

It may also be possible to compare against a control group receiving individual vaccines at

different time points. It is advisable to consult PMDA in advance about the study design (timing of evaluation, etc.) for a study with a control group receiving individual vaccines at different timings.

Question 7 The Guidelines state that "If the antibody titer against any of the antigens following vaccination with the combined vaccine is lower than the corresponding antibody titer when the individual vaccines are administered at different time points or administered at different sites simultaneously, it is required to provide reasons and data supporting the view that there is no problem in the clinical protective effect of the combined vaccine." If it is difficult in Japan to examine the protective efficacy, such as when an approved single-antigen vaccine is used for routine vaccination, what kind of explanation is supposed to be presented?

(Answer)

When the antibody level required for protection is known, such information can be used. In addition, other existing information (that of similar drugs or overseas information) may be used on a case-by-case basis.

3.5. Discussions on the development of vaccines for children and simultaneous vaccination

Question 8 When recipients of routine vaccinations have to be included in a clinical trial, there is a concern that especially in children, many routine vaccines are administered. In such cases, is it necessary to investigate the influence of the vaccine under development on the effectiveness (immunogenicity) and safety of all routine vaccines that can be administered simultaneously?

(Answer)

For vaccines that are expected to be primarily administered to children of a certain age, such as infants, it is recommended to investigate the mutual effects of the vaccines that can be administered simultaneously and the vaccine under development. In this investigation, existing information in Japan and overseas (epidemiological information, study results, etc. published in the literature or other sources) may be utilized.

3.7. Investigation of the route of administration

Question 9 The Guidelines state that when a new route of administration is developed, it needs to be supported by results from Japanese clinical trials. Is it necessary to conduct a clinical trial comparing the new route with the existing route?

(Answer)

For vaccines for which both new and existing routes of administration have extensive experience in Japan as vaccination routes, such as subcutaneous and intramuscular routes, and

for which the protective efficacy of the vaccine can be explained through a surrogate measure such as immunogenicity including in overseas clinical trials, the efficacy with the new dosing route may be supported by comparing the results regarding the surrogate measure in an uncontrolled Japanese study for the new dosing route with the results from confirmatory studies with the existing dosing route.

However, when developing a vaccination route with little experience such as intranasal vaccination, it is advisable to consult PMDA about the necessary study at an early stage of development.

3.8. Discussions on the vaccination schedule

Question 10 For example, if a study to investigate the efficacy (including immunogenicity) and safety of a vaccine with a booster dosing 6 to 18 months after the primary immunization is conducted, is a study design to file a marketing application with the results of the primary immunization and subsequently file another application for the booster immunization (2 applications in total) acceptable?

(Answer)

When the necessity of a booster dose in a relatively short period (about 6 months to 1 year and a half) after the primary immunization is known beforehand, it is desirable to submit the marketing application with the results of booster dosing to allow for overall evaluation of the dosage including for the booster and review of the clinical positioning and to exclude duplicate tasks for the preparations of materials for the post-marketing survey plan and the proper use guide, as well as their consideration.

4.3.3. Discussions on duration of protection and booster immunization

Question 11 The Guidelines state that "In some cases, it is unfeasible to investigate the duration of the protective effect of the vaccine or evaluate booster doses before marketing authorization." What should be considered when a booster immunization is developed after marketing authorization of the vaccine?

(Answer)

The necessity and appropriate timing of booster immunization can be examined based on the results of post-marketing surveys/clinical studies, epidemiological studies, etc. When the need for booster immunization is suggested, the efficacy, etc. of booster immunization should be examined in clinical studies. In such cases, Section 4.3. "Efficacy evaluation" in the Guidelines can still be helpful.

4.4.1. Adverse events and expected local and systemic reactions

Question 12 What is the immunization stress-related response (ISRR)? Are there any actions one can take for it?

(Answer)

ISRR refers to a range of responses triggered by vaccination-related stress. Refer to the WHO website (https://www.who.int/publications/i/item/9789241515948) and the document posted (IMMUNIZATION STRESS-RELATED RESPONSES) for a detailed definition and strategies to address ISSR.

5. Statistical Considerations

Question 13 The protocol for an active-control, phase III study to confirm non-inferiority to an existing similar drug is required to specify the lower equivalence margin ("3.3.2 Trials to Show Equivalence or Non-inferiority" in Statistical Principles for Clinical Trials (ICH E9 Guideline) (PMSB/ELD Notification No. 1047, issued by the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare, dated November 30, 1998)). When the endpoint for the approved control vaccine is the seroprotection rate or seroconversion rate, how should a non-inferiority margin (lower equivalence margin) be determined?

(Answer)

In determining the non-inferiority margin, it is required to explain whether the equivalence margin determined is acceptable from clinical viewpoints such as infectious disease epidemiology and disease characteristics. The following statement in Guidelines issued by the WHO (Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations) can be helpful: "When it is proposed to demonstrate non-inferiority between vaccine groups based on GMT or GMC ratios for antibody titers or concentrations it is suggested that the lower bound of the 95% confidence interval around the ratio (test versus reference vaccine) should not fall below 0.67."

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