(Attachment)

Guidelines for Clinical Studies of Vaccines for Infectious Disease Prevention

Revised on March 27, 2024

1. Introduction

Vaccines are pharmaceutical products that exert their effect by activating the immune system using specific antigens as its targets. While most vaccines aim to prevent the onset of infectious diseases or of infections (hereinafter referred to as "infectious disease prevention") in individuals, they can also potentially achieve herd immunity effects, where an outbreak can be averted within a community as a whole in addition to the vaccinated individuals when a sufficient proportion of the community acquires immunity. These Guidelines apply to the development of vaccines for infectious disease prevention and do not apply to "therapeutic vaccines" such as anti-tumor vaccines (cancer vaccines) and anti-idiotypic vaccines (including monoclonal antibodies used as immunogens). Vaccines for infectious disease prevention covered by these Guidelines (hereinafter referred to as "vaccines") are those inducing specific immunity against infectious pathogens and include:

1. Vaccines containing, as active ingredients, chemically or physically inactivated microorganisms, maintaining their immunogenicity (such as Japanese encephalitis vaccine),
2. Vaccines containing as active ingredients either microorganisms antigenically similar to human pathogens, or attenuated microorganisms that maintain appropriate immunogenicity (such as measles vaccine, BCG vaccine, etc.),
3. Vaccines containing as active ingredients either antigens extracted from pathogenic microorganisms or toxoids that have been obtained by inactivating toxins produced by pathogenic microorganisms (such as influenza HA vaccine, pertussis vaccine, diphtheria toxoid, tetanus toxoid, etc.),
4. Vaccines containing as active ingredients antigens obtained through genetic engineering techniques, or these antigens aggregated, polymerized, or conjugated to carriers (such as hepatitis B vaccine, pneumococcal conjugate vaccine, etc.),
5. Vaccines obtained by modifying genes of microorganisms such as viruses and bacteria, and
6. Vaccines containing, as active ingredients, nucleic acids such as expression plasmids.

If other guidelines relevant to the vaccine under development have been issued, they must also be addressed.

In the development of novel vaccines not included in the above, it is advisable to start consultations with regulatory authorities from an early stage of development after summarizing

available findings.

Because vaccines exert their effect by activating immunity and are administered mainly for the purpose of preventing infectious diseases in healthy individuals, they have characteristics different from other drugs, such as different risk-benefit balance profiles from general therapeutic drugs. Guidelines by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and other existing guidelines are also useful in clinical studies of vaccines for reference, but there are aspects that require special considerations for clinical development of vaccines due to their unique characteristics described above. The present Guidelines outline the current standard methods for planning, conducting, and evaluations in clinical trials to assess the efficacy and safety of pharmaceuticals developed as vaccines, taking into account the unique characteristics of vaccines.

2. Protection of Study Subjects

Clinical trials must be conducted according to the Ministerial Ordinance on Good Clinical Practice for Drugs (GCP) that is based on the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices. Post-marketing clinical studies or surveys must be conducted according to the Ministerial Ordinance on Good Post-marketing Study Practice for drugs (GPSP)". The principle of the Declaration of Helsinki, "Protection of Human Rights, Maintenance of Safety, and Improvement of Welfare", is assured through compliance with GCP and GPSP. Any clinical study must undergo a review and be approved as required by law prior to its initiation. In addition, appropriate informed consent must be obtained from the subjects participating in clinical studies. When it is difficult to obtain informed consent from a prospective participant due to their lack of capacity to provide consent, the participant may be enrolled in a clinical trial by obtaining written informed consent from their legally acceptable representative (defined as a person who exercises parental authority over the participant, a spouse, a guardian, or other person of equivalent status). Particular attention should be paid to ethical considerations in clinical studies in infants, children, pregnant women, and the elderly. In particular, as for informed assent in pediatric studies, etc., refer to Clinical Investigation of Medicinal Products in the Pediatric Population (PMSB/ELD Notification No. 1334 issued by the Director of Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare, dated December 15, 2000) (ICH E11 Guideline).

3. Considerations for Clinical Development

3.1. Phases of clinical development

3.1.1. Phase I studies

Phase I studies are generally small-scale studies and designed for preliminary exploration of vaccine safety and immunogenicity. The doses and vaccination methods used for phase II studies and later development are determined based on information including that of the results from the phase I studies conducted up to that point. Pharmacokinetic studies are generally not

required for vaccine development. However, if a novel substance such as a novel adjuvant is contained, pharmacokinetic studies may be required for the novel substance. For novel live attenuated vaccines and recombinant live vaccines, it should be determined whether or not studies for possibility of vaccine shedding, etc. are required, based on information on target infectious diseases and the microorganism (such as virus) from which the vaccine is derived, results from nonclinical studies, etc. Pharmacodynamic studies include immunogenicity studies to characterize the immune response to the vaccine.

In general, phase I studies should be conducted in Japanese healthy adult volunteers at sites where the safety of subjects is ensured and appropriate laboratory tests are available with careful monitoring. However, the conduct of phase I studies in Japanese healthy adults may not be required in cases such as where the below-mentioned Japanese clinical study for using overseas clinical study data will be conducted or where appropriate overseas clinical study data are available in the development of a vaccine for specific populations such as children and the elderly.

To understand the relationship between adverse events and a vaccine, it is desirable to include an appropriate control group using a placebo or existing similar drugs also in phase I studies. For optimal safety evaluation, the concomitant use of other vaccines or medications should be avoided if possible. Laboratory tests should be performed on subjects to collect basic information on the safety and efficacy of the vaccine. When conducting a first-in-human study, refer to the Notification on Revision of Guidance for Safety Assurance in First-in-Human Studies during Drug Development (PSEHB/PED Notification No. 1225-1 issued by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated December 25, 2019).

The evaluation items for the safety evaluation of attenuated live vaccines and recombinant live vaccines should include shedding of the vaccine strain from subjects, the possibility of transmission to third parties who have been in contact with subjects, the genetic stability of the vaccine strain, and possibility of mutation to virulent strains. Clinical studies of live attenuated vaccines and recombinant live vaccines must be conducted at appropriate facilities depending on the risk of transmission of the shed vaccine strain to individuals other than study subjects. For vaccine strains that will be shed from subjects, ICH Opinion: Basic Principles on Virus and Vector Shedding (Administrative Notice of the Office of Counsellor for Medical Devices and Regenerative Medicine Products, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated June 23, 2015) may be helpful.

3.1.2. Phase II studies

The objective of a phase II study for a vaccine is to determine the dose and basic dosing schedule of the vaccine that will be used in phase III studies, using immunogenicity and safety as measures. Phase II studies may also be conducted to analyze various parameters related to immune responses, such as subject age, sex, maternal antibodies, and prevaccination antibody

titers. Factors that should be evaluated regarding their impact on immune response include (1) the amount of vaccine administered, (2) the dosing interval, (3) the number of doses, and (4) the route of administration. It is also desirable to investigate the duration of immunity, the need for booster immunization, and quantitative aspects of the immune response. More than one study may be needed to obtain sufficient information.

In the case of a vaccine with a novel antigen, etc., the dose and dosing schedule are important considerations, and dose-response data in the target population should be obtained. If a Japanese clinical study is to be conducted with reference to a dosage established overseas, it is required to explain that the proposed dosage is appropriate for the Japanese population. When the immune response affecting prevention of the clinical events including disease onset, based on the characteristics of the disease (hereinafter referred to as the 'protective efficacy or the like') has not been clearly understood, it is important to identify the antigen level at which immune response doesn't significantly increase in the antigen uptake.

Analyses of immune response based on vaccination are also an important part of phase II studies and should be carefully evaluated. In particular, for vaccines for which the relationship between the protective efficacy or the like and immune response is not clear, immunological characteristics should be investigated in detail as much as possible.

When conducting clinical studies of live attenuated vaccines or replication-competent recombinant live vaccines, it is recommended to include a follow-up period of at least 4 weeks after vaccination. If shedding of the vaccine strain, transmission to individuals other than subjects, a possibility of gene alteration of the vaccine strain, etc. have been demonstrated in the phase I studies, a follow-up period and observation items should be determined based on these results so that risks such as shedding, transmission, and gene alteration of live vaccines, etc. can be appropriately observed.

For a clinical development of a combined vaccine consisting of vaccines that have already been approved in Japan and have sufficient clinical experience, the need for phase II studies may be obviated if appropriate information on dosage has been obtained in phase I studies.

3.1.3. Phase III studies

A phase III study is a clinical study that is designed, taking into account actual conditions of clinical use, to obtain efficacy and safety data of the vaccine, and is usually conducted in a large population.

In a phase III study to confirm the clinical efficacy of a vaccine, it is basically desirable to verify the efficacy of the vaccine using the protective efficacy or the like observed when the vaccine is administered through the intended route of administration with the intended dosage as an endpoint in subjects who appropriately reflect the target population in practical use, and it is desirable to conduct a randomized double-blind comparative study with an appropriate control group. When conducting a phase III study using the protective efficacy as an endpoint, it should be noted that the epidemic status of infection in the region and/or at the timing of study

may affect the feasibility of the study. In addition, in some cases, it may be appropriate to consider a global clinical trial described in Section 3.3, because enrolling a larger number of subjects is generally required when assessing the protective efficacy, compared to when assessing the cure or improvements of symptoms. On the other hand, as exemplified in Section 4.3.1, in cases such as when the incidence of disease is very low, it is often difficult to evaluate the protective efficacy or the like as an efficacy endpoint. In such a case, it is necessary to take a different approach depending on the nature of disease; for example, a study design to evaluate a surrogate measure such as an antibody titer for which a relationship with the protective efficacy or the like has been established may be appropriate. For the measurement of the surrogate, using a standard test method with demonstrated reproducibility is required. In phase III studies, it is important to strictly evaluate the risk-benefit balance of the vaccine and demonstrate its usefulness.

3.1.4. Post-marketing activities

In general, the safety and efficacy information that can be obtained from clinical studies conducted before marketing authorization is limited. For this reason, it is necessary to, taking into account matters that could not be adequately assessed at the development stage and the potential risks suggested at the same stage, clarify whether there is lacking information that should be collected after the market launch and, if any, what information should be collected, and formulate an appropriate drug risk management plan.

When considering pharmacovigilance activities, a Safety Specification should be developed taking into account the characteristics of the vaccine and the target population as well as the information obtained from clinical studies. On that basis, for each risk identified in the Safety Specification, concerns to be managed after the market launch should be clarified, and the scientifically most appropriate measures to resolve the concern should be determined according to the characteristics of the concerns. For example, post-marketing surveillance and other studies/surveys are conducted to clarify the causal relationship with a vaccine for risks, which has been suggested in the development stage and/or overseas practical use.

Surveys/studies on effectiveness are conducted to investigate aspects that were not sufficiently evaluated in clinical trials (examples listed below). Such a survey/study can also be important in cases such as where it was difficult to clearly evaluate the protective efficacy or the like in phase III studies because of a low incidence of the target infectious diseases.

1. Investigation of the effectiveness in special risk groups (such as the elderly, immunocompromised patients, and patients with specific diseases)
2. Long-term assessment of endpoints such as the persistence of vaccine effectiveness
3. Investigation of cases such as where new variant strains of an infectious pathogen with different characteristics (antigenicity, etc.) have emerged and persistence of the effectiveness of the current product is questioned

When developing implementation plans for post-marketing surveillance and other

studies/surveys, refer to Approach to Developing Implementation Plans for Post-Marketing Surveillance and Other Studies of Pharmaceuticals (PSEHB/PED Notification No. 0314-4 and PSEHB/PSD Notification No. 0314-4, issued jointly by the Director of Pharmaceutical Evaluation Division and Director of Pharmaceutical Safety Division, PSEHB, MHLW, dated March 14, 2019), as well.

3.2. Japanese clinical studies for using overseas clinical study data

For vaccines for which there is a known surrogate measure such as an immunological endpoint for which a relationship with the protective efficacy or the like has been established and the efficacy can be explained from the results of evaluations with the surrogate measure, data such as those from large-scale overseas clinical trials may be used to support the marketing application by conducting Japanese studies to evaluate appropriate endpoints such as immunogenicity.

When conducting a Japanese clinical study for using overseas clinical trial data, it is necessary to sufficiently explain the appropriateness of using overseas clinical data and the appropriateness of the plan for the Japanese clinical study, taking into account Ethnic Factors in the Acceptability of Foreign Clinical Data (ICH E5 Guideline) and the following points:

1. Ethnic differences in the efficacy and safety of the vaccine between the Japanese and the ethnic groups in overseas clinical trials, as measured by the protective efficacy or the like.
2. Differences in vaccination schedule, dose, route of administration, control drug or concomitant vaccine between the overseas clinical trials and the Japanese clinical study.
3. Differences in epidemic status, epidemic strains or serotype distribution of target infectious diseases between Japan and overseas.

Note that for vaccines, pharmacokinetics is not usually assessed, and therefore what is described here is not necessarily consistent with the concept of bridging described in the ICH E5 Guideline that is based on pharmacokinetic data.

When there is a surrogate measure, such as antibody titer, for which a relationship with the protective efficacy or the like has been established and overseas clinical data obtained using such a measure are employed, the measure used in the Japanese clinical study should be measured using the same method as that used in the overseas clinical trials, in order to minimize differences caused by the measurement method. It is desirable to perform measurements using international standard substances and standard reagents.

3.3. Global clinical trials

Global clinical trials are, unlike Japanese clinical trials, conducted in various regions and ethnicities and need to be planned while taking into account ethnic factors. Therefore, considering the aspects described in the ICH E5 Guideline is useful also in planning global clinical trials. Refer also to Basic Principles on Global Clinical Trials (PFSB/ELD Notification

No. 0928010, by the Director of Evaluation and Licensing Division, PFSB, MHLW, dated September 28, 2007), Basic Principles for Conducting Phase I Clinical Trials in Japanese Subjects Prior to Initiating Global Clinical Trials for Drugs with Advanced Clinical Development Overseas" (PFSB/PED Notification No. 1225-2, by the Director of the Pharmaceutical Evaluation Division, PFSB, MHLW, dated December 25, 2023), and General Principles for Planning and Design of Multi-Regional Clinical Trials (ICH E17 Guideline) (PSEHB/PED Notification No. 0612-1, by the Director of the Pharmaceutical Evaluation Division, PSEHB, MHLW, dated June 12, 2018).

The three points described in Section 3.2 should be considered, as well.

When conducting a Japanese clinical trial prior to a global clinical trial, it is desirable to evaluate the safety in the Japanese population, assess the efficacy based on factors such as immunogenicity, and then compare these results with data from overseas clinical trials to corroborate the decision on whether Japan can participate in the global trial.

3.4. Special Discussions on Clinical Studies of Combined Vaccines

In these Guidelines, a combined vaccine refers to a vaccine containing antigens (or the like) for multiple infections as active ingredients (e.g., pertussis-diphtheria-tetanus combined vaccine, measles-rubella combined vaccine). Note that for multivalent vaccines containing multiple serotypes of an antigen for the same infection as active ingredients (such as pneumococcal vaccines), the descriptions about combined vaccines in this document may be applicable.

Clinical studies of combined vaccines are conducted to evaluate the efficacy of each antigen and the safety of the combined vaccine. In combined vaccines, there is a possibility of interference, inhibition, interaction, or synergistic reactions between the components of a vaccine. Therefore, the efficacy and safety in clinical studies should be compared with an appropriate control group. For example, when individual vaccines for the antigens comprising a combined vaccine are approved in Japan, the combined vaccine should, in principle, be compared against a control group receiving simultaneous administration of the individual vaccines. Given that existing information on between-antigen interference and other interactions may be applicable in some cases, it is advisable to reach an agreement with regulatory authorities on the aspects to be examined and the study design during the planning phase of the clinical trial.

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 the dose or vaccination schedule is changed as a result of switching from existing individual vaccines to a novel combined vaccine, the rationale for this should be explained based on

scientific evidence.

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

In the development of vaccines for children, those who are receiving routine vaccinations may have to be enrolled in a clinical trial. The study design should be determined so that the influences of the vaccine under development on the effectiveness (including immunogenicity) and safety of the routine vaccines as well as other interactive effects are specified. When there are concerns about immunological interference and safety interactions during simultaneous administration of a routine vaccine and a vaccine under development, one approach is to compare the efficacy (including immunogenicity) and safety between a group receiving only the routine vaccine and a group receiving both the routine vaccine and the vaccine under development concurrently. For the primary immunization in infants, attention should be paid to the possibility of immune interference by maternal antibodies.

3.6. Extension of indication to populations requiring special attention to efficacy and safety evaluation such as the immunocompromised population

When the indication is to be extended, in addition to the major target population for vaccination, to populations requiring special attention to the evaluation of efficacy and safety, such as immunocompromised individuals and pregnant women, the extension can be evaluated by comparing the results for the efficacy (including immunogenicity) and safety in the confirmatory studies in the major target population and results from clinical studies in these populations. For the development for these populations, it is advisable to confirm the vaccination needs from an early stage of vaccine development and take appropriate actions.

3.7. Investigation of the route of administration

Vaccines can be administered through various routes, such as subcutaneous injection, intramuscular injection, oral route, intranasal route, and intradermal injection, depending on the characteristics of the formulation. In principle, the route of administration proposed in a marketing application needs to be supported by results from Japanese clinical trials. However, if the product is developed with more than one administration route, Japanese confirmatory studies are not always needed for all the administration routes. As for the efficacy (including immunogenicity) and safety for the administration route for which no confirmatory study is conducted, it is necessary to compare the results of the clinical studies conducted with this route and the results of efficacy (including immunogenicity) and safety for the administration route that was examined in the confirmatory study, and explain that the efficacy (including immunogenicity) and safety are not significantly different for these routes. In Japan, subcutaneous injection has been commonly used as the vaccination route. Overseas, intramuscular injection is commonly used for inactivated vaccines, and subcutaneous injection

for live vaccines. Considering the recent demand for inactivated vaccines to be administered intramuscularly as an additional option, as is done overseas, it is advisable to evaluate the routes of administration in Japan from the early stages of development.

3.8. Discussions on the vaccination schedule

Vaccines may require multiple doses to induce an innate immune response as the primary immunization. Therefore, it is necessary to obtain data on the efficacy (including immunogenicity) and safety after consideration for the appropriate number of doses and timing of administration beforehand with reference to the results of nonclinical studies and vaccination schedules of similar drugs. To establish an appropriate vaccination schedule, it is advisable to consider not only the aspects of efficacy and safety but also whether the vaccination schedule is convenient for providers and recipients of the vaccine. In addition, the necessity of booster administration to maintain the vaccine effect for a longer period and, if possible, whether immunological memory is induced should be considered. Whether immune memory is induced following the primary immunization may be investigated, for example, by administering a booster dose after an interval of at least 6 to 18 months after the primary immunization and assessing the efficacy (including immunogenicity) and safety.

4. Considerations for Clinical Studies

4.1. Definition of disease onset

The definition of disease onset is important when evaluating the efficacy of the vaccine based on clinical protective effect. In addition, the rationale for the definition of disease onset should be provided. Similarly, the sensitivity and specificity of the confirmation method for disease onset are important. When diagnosis is to be made based on predefined clinical criteria, justification and evaluations that support these criteria are required. Diagnosis based on intralaboratory diagnostic testing (antibody detection, antigen detection, etc.) and/or laboratory testing should be performed as much as possible to support the clinical definition of disease onset.

4.2. Discussions on control groups

In clinical studies, it is desirable to include a control group to investigate the incidence of adverse events, etc. In general, a placebo control group refers to a control group that receives a formulation without the test antigen. If there is an existing vaccine used for prevention of the same infections as the vaccine to be developed, a comparative study with this existing vaccine should be considered. In the development of combined and multivalent vaccines, if no such existing vaccine is available, comparative studies with approved vaccines containing all antigens other than the newly added antigen(s) should be considered. If a control group is included, the study should be conducted in a blinded manner as much as possible.

4.3. Efficacy evaluation

In principle, the efficacy of vaccines should be evaluated using the protective efficacy or the like as the primary endpoint. Studies using the protective efficacy or the like as a clinical endpoint must be conducted in regions and timings where a certain degree of spontaneous infection is present and comparative studies can be conducted. On the other hand, if a relationship is established between the protective efficacy or the like and the antibody (titer) induced by the vaccine or other specific biological markers, these may be used as alternative primary endpoints. If such a surrogate measure is used, its validity must be scientifically discussed. In principle, immunogenicity must be assessed in all clinical studies.

For a multivalent vaccine composed of multiple strains or serotypes, it is desirable for the primary efficacy endpoint to be the prevention of individual infections or the alleviation of symptoms caused by the various strains or serotypes contained in the vaccine. However, if there is an appropriate surrogate measure, it can be used for evaluation. It is desirable to plan clinical studies so that the efficacy against each strain or serotype epidemic in the region where the study is conducted can be evaluated to a certain extent.

4.3.1. Discussions on clinical trials assessing the protective efficacy or the like

In principle, the clinical efficacy of vaccines should be evaluated using the protective efficacy or the like as an endpoint. For example, the protective efficacy of a vaccine is defined as the reduction rate of the disease incidence in the vaccinated group relative to the non-vaccinated group (see "Protective efficacy of vaccines" in "Glossary"). Ideally, evaluation of the protective efficacy or the like of a novel vaccine should be completed before the marketing application. However, there may be situations, as exemplified below, where those evaluations are not feasible to conduct prior to marketing authorization. In these cases, it is necessary to consult the appropriate regulatory authorities on the clinical trials that are required for the marketing application and reach an agreement.

1. It is practically impossible to assess the protective efficacy when no potentially preventable infection occurs during the study period (e.g., smallpox) or when they occur only at a very low incidence (e.g. brucellosis, Q-fever), even if the clinical trial is conducted with a reasonable study period. In other cases, the occurrence of infection is unpredictable, and there is a tendency to become epidemic temporarily, and therefore the protective efficacy of vaccines cannot be evaluated (e.g., some viral hemorrhagic fever).
2. Cases where it is impossible to conduct clinical trials to assess the protective efficacy or the like, and there is no known immunological endpoint for which a relationship with the protective efficacy or the like has been established. In such cases, it is considered sometimes appropriate to evaluate the possibility of the protective efficacy or the like of the vaccine by comparing the immune responses with those observed in previous studies of similar vaccines for which the protective efficacy or the like has already been proven.
3. Cases where it is impossible to conduct clinical trials to assess the protective efficacy or

the like, there is no known immunological endpoint for which a relationship with the protective efficacy or the like has been established, and there are no available immunological data from past studies that can be used for comparisons (e.g., anthrax).

4.3.2. Discussions on immunological endpoints associated with the protective efficacy or the like

In some situations where the target population is widely immunized with already-marketed vaccines and the incidence of the clinical events associated with the target disease has been highly decreased, the efficacy of a vaccine under development cannot be evaluated by the difference in the incidence of those clinical events. When there is a known immunological endpoint for which a relationship with the protective efficacy or the like has been established, trials to evaluate the immune response should be conducted. When there is a foreign confirmatory study that has assessed the protective efficacy of the vaccine, and if this study can be used based on Section 3.2 of these Guidelines, it may be possible to conduct a Japanese study on immunogenicity using an appropriate measure and refer to the overseas clinical study. For some existing vaccines, vaccine-induced immune responses associated with the protective efficacy or the like have been identified; demonstrating the efficacy of vaccines using these immune responses has been generally accepted.

For existing vaccines for which no immune responses scientifically related to the protective efficacy or the like have been identified, or for vaccines using novel antigens, efforts should be made to identify immune responses associated with the protective efficacy or the like as much as possible during confirmatory clinical trials to evaluate efficacy. Therefore, clinical trials that allow for assessment of the immune responses associated with the protective efficacy or the like should be designed. However, for some infectious diseases it may be difficult to assess the immune responses associated with the vaccine's protective efficacy or the like. In these cases, immunological responses possibly related to the vaccine's protective efficacy or the like should be examined after marketing authorization, and the relationship between the immunological responses and the short-term or long-term protective efficacy should be elucidated based on the examination results.

When established animal infection models are available, it is also useful to predict the immune responses associated with the protective efficacy or the like in humans through challenge studies. Efforts should also be made to establish animal models of infections that are susceptible to infectious pathogens and have a pathogenic mechanism similar to that in humans, such as some transgenic animals.

These immune responses associated with the protective efficacy or the like are generally represented by functional antibody titers (such as neutralizing antibody titers) with neutralizing effects or inactivating effects against infectious factors or toxins. However, when there is a clear relationship between the functional antibody titer and an antibody titer measured by an assay method such as ELISA (enzyme-linked immunosorbent assay) or HI (hemagglutination

inhibition), these can be used as an alternative. Antibody titers are assessed using entities such as the inverse cumulative frequency distribution and the geometric mean antibody titer.

For certain antigens expected to elicit a cellular immune response, if the cellular immune response is predicted to be an important or essential response for the overall immune response to the antigen, it is recommended to design a clinical study that allows for investigation of the relationship between disease prevention and the cellular immune response.

4.3.3. Discussions on duration of protection and booster immunization

In some cases, it is unfeasible to investigate the duration of the protective effect of the vaccine or evaluate booster doses before marketing authorization. In general, it is often impossible to extend the duration of clinical trials for the purpose of investigating the clinically effective period of a vaccine. In post-marketing surveillance and other studies, consideration should be given to examining the long-term protective effects and the necessity for booster immunization. For newly developed vaccines, information on the relationship between time course of antibody titer and protective efficacy, the type of antibodies induced, induction of immunological memory, etc. is important to infer the duration of vaccine effect and the appropriateness of the timing of booster immunization.

4.3.4. Discussions on the trial size

In clinical trials to evaluate the efficacy of vaccines, the sample size should be determined based on the occurrence of infectious diseases, the clinical endpoints, the immune responses associated with the protective efficacy or the like (if any), etc. so that statistically appropriate evaluations can be performed.

4.4. Safety evaluation

The safety evaluation during clinical development prior to the marketing authorization application aims to clarify and quantify the safety profile of the vaccine throughout the entire development program and is conducted in alignment with its intended use after marketing. When safety issues are identified in nonclinical studies, particular attention should be paid to them in clinical studies.

Safety evaluation must be conducted in all enrolled subjects who received the vaccine in clinical studies, and safety data should be collected from the time of administration. Safety data should be collected at least after each administration. Most of the expected local/systemic reactions to vaccines occur within a few days after administration. The collection of unexpected adverse events is also important. The guideline for the duration of adverse event collection is approximately 2 weeks after administration for inactivated vaccines and 4 weeks after administration for live vaccines. However, it may be necessary to set an appropriate period of 2 to 4 weeks or longer depending on the characteristics of the vaccine; for example, a follow-up period of 1 year after administration can be appropriate for vaccines with a new modality or

a novel antigen. Adverse events may be collected from the records in the subject diary using methods such as by telephone, in each site visit in the administration, or electronically. In some cases, it is necessary to collect adverse events that occur beyond the specified period. When a follow-up period after the final administration has been set, the rationale for the period needs to be explained.

The collection of data for comparison with an active control drug (vaccine used for prevention of the same infection) with similar antigens should also be considered. When comparative data are collected, adverse events that occurred should be thoroughly analyzed to investigate the differences stemming from the characteristics of the drug product. In addition, clinically significant interactions with other vaccines, and drugs and factors affecting safety, such as age and epidemiological characteristics, should be investigated.

4.4.1. Adverse events and expected local and systemic reactions

An adverse event (AE) is any unfavorable and unintended sign, symptom, or disease occurring in a subject who has received an investigational product (an approved product for post-marketing surveillance), whether or not it is considered related to the investigational product. Adverse events for which a causal relationship cannot be ruled out will be handled as adverse drug reactions. Due to the characteristics of a vaccine that is administered as a medicine to induce immunity to prevent diseases, vaccines often induce undesirable local reactions such as swelling, redness, and pain at the injection site and systemic reactions such as pyrexia and swollen lymph nodes, at the same time with expected immunogenicity. These side effects are called adverse reactions. Because the expected local reactions and systemic reactions differ depending on the modality, route of administration, etc. of the vaccine, they should be identified at an early stage of clinical development and a grading of each reaction should be defined.

Also, clinical trials of vaccines must be conducted with attention to the possible occurrence of immunization stress-related response (ISRR).

4.4.2. Serious adverse events (SAEs)

A serious adverse event (SAE) is an AE that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is a medically important event.

A detailed report should be prepared for all SAEs that occur during the post-vaccination observation period. Full monitoring is required for SAEs reported after the end of the post-vaccination observation period. It is important to continue to collect post-marketing information because some post-vaccination SAEs rarely occur and may not be found during the clinical trial.

5. Statistical Considerations

For general statistical considerations for clinical trials, refer to Statistical Principles for

Clinical Trials (ICH E9 Guideline) (PMSB/ELD Notification No. 1047, issued by the Director of ELD, PMSB, MHW, dated November 30, 1998).

Glossary

Adjuvant

A pharmaceutical aid to facilitate immune response. A substance that nonspecifically enhances the immune response to the antigen co-administered *in vivo.*

Geometric mean titer (GMT)

For a group consisting of n subjects, the GMT is given by the n-th root of the product of the tiers (Xn) for all subjects, i.e., n√ X1×X2×•.••×Xn.

Primary immunization

A first series of vaccine administration during a prespecified period (usually, the dosing interval is 6 months or shorter). The effect to induce immunological memory is called the priming effect. Once innate immune activation and memory immune cells have been induced, these memory cells persist and a single additional dose (booster) is expected to effectively induce immunity within a short period.

Hemagglutination inhibition (HI) assay

Viruses such as influenza virus, measles virus, rubella virus, and Japanese encephalitis virus have a protein (hemagglutinin; HA) that binds to red blood cells. This property has been used to measure antibodies. Individuals infected with these viruses have antibodies (HI antibodies) against virus hemagglutinin. The method of antibody measurement is as follows: First, the virus antigen and the test serum are reacted, and then animal blood cells are added to the mixture. Virus antigen molecules that remain unreacted with antibodies react with red blood cells, and red blood cells agglutinate. The antibody titer is expressed as the maximum dilution factor that inhibits the hemagglutination of red blood cells.

Neutralizing antibody

An antibody that neutralizes viral infectivity or toxin activity. In viral infections, it directly acts to prevent infection. To measure neutralizing antibodies, the virus and the test serum are allowed to react, then the mixed solution of virus and serum is allowed to infect cultured cells, and the replication of the unreacted (not neutralized) residual virus particles is determined. The neutralizing antibody titer is expressed as the maximum dilution factor that inhibits viral replication.

Booster immunization

Vaccination given after a certain period of time (usually for 6 to 18 months) following the primary immunization for the purpose of inducing a long-term disease prevention effect.

Disease prevention

To prevent the onset of diseases caused by infection with pathogenic microorganisms.

Immunogenicity

The ability of the vaccine to induce an immune response (e.g., humoral, cell-mediated, and immunological memory).

Immune memory

Immune memory is established from the initial response to a specific pathogen; upon subsequent encounters with the same pathogen, it enables the immune system to mount a faster and more robust response (secondary immune response).

Protective efficacy of vaccines (vaccine efficacy)

The protective efficacy of vaccines is expressed as the percent reduction of the attack rate (incidence of disease onset) in the vaccinated group relative to in the non-vaccinated group, and assessed with the direct defense (that is, defense attributable to vaccination in vaccinated group). The protective efficacy of vaccines (vaccine efficacy; VE) is, in general, calculated as:

VE = (ARU-ARV)/ARU×100% = (1-ARV/ARU)×100% = (1-RR)×100%

ARU = attack rate in unvaccinated (control group)

ARV = attack rate in vaccinated group

RR = relative risk = risk ratio (RR is adjusted by the observation period in each group)

(Source: WHO Guidelines on Clinical Evaluation of Vaccines)