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To: Directors of Prefectural Health Departments (Bureaus)

Director, Evaluation and Licensing Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare

(Official seal omitted)

Guidance on Clinical Evaluation of Travelers' Vaccines, etc.

Guidance on the clinical evaluation of travelers' vaccines, etc. has been formulated as shown in the attachment. Please inform related parties under your jurisdiction of this notification.

This guideline provides basic principles based on the knowledge of current scientific findings. Therefore, it is not necessary to follow the methods described in the guideline strictly as long as their alternative methods are properly rationalized by the advancement of academic knowledge.

ATTACHMENT

Guidance on Clinical Evaluation of Travelers' Vaccines, etc.

1. INTRODUCTION

A rapid increase in the number of overseas travelers has increased the demand for vaccines to prevent infectious diseases in people traveling overseas in recent years. However, some of the vaccines recommended for overseas travelers by the World Health Organization (WHO)[1)] have not been launched yet in Japan. In addition, because of reported cases of sporadic infection in Japan due to the influx of infectious diseases such as dengue fever, which has not been epidemic in Japan, there has been an increasing need for preventive vaccines against infectious diseases that have not occurred or are rare in Japan. It is hoped that these vaccines will be put into practical use without falling behind the world.

Especially for the development of vaccines against infectious diseases that occur or spread in countries or regions other than Japan (hereinafter referred to as "travelers' vaccines, etc."), it is difficult to conduct clinical studies to evaluate their preventive effect in Japan because of a small or no number of events of such infectious diseases. For vaccine development in Japan, therefore, the principles of clinical evaluation are considered different between vaccines against infectious diseases prevalent in Japan and travelers' vaccines, etc.

It is meaningful to take this difference into account to promote smooth and efficient clinical development of travelers' vaccines, etc. This guidance provides points to consider for the clinical evaluation of travelers' vaccines, etc. for their smooth development in order to supplement the "Guidelines for Clinical Studies of Preventive Vaccine for Infectious Diseases" (hereinafter referred to as "Guidelines for Preventive Vaccine for Infectious Diseases").[2)]

2. PURPOSE

This guidance summarizes the principles of clinical evaluation of travelers' vaccines, etc. and points to consider for their smooth development. It should be noted that this guidance has been formulated based on the current scientific level and may be changed as the scientific level changes in the future.

3. SCOPE

This guidance applies to preventive vaccines against infectious diseases that pose an infection risk to overseas travelers. However, the principles may be applicable to preventive vaccines against infectious diseases that do not occur or are rare in Japan when their administration is considered not only in overseas travelers but also in people living in Japan.

For the clinical evaluation of vaccines that are developed as a part of measures against novel influenza, the "Guideline on the Development of Prototype Vaccine against Pandemic Influenza"[3)] should be referenced, instead of this guidance.

4 PRINCIPLES OF DEVELOPMENT

Preventive vaccines against infectious diseases are evaluated for their clinical efficacy and safety in various clinical studies. For the clinical evaluation of travelers' vaccines, etc., the basic requirements and data required for approval application are not different from those described in the Guidelines for Preventive Vaccine for Infectious Diseases.

In the development of pharmaceuticals including vaccines, clinical development in adults usually precedes clinical development in children. In endemic areas, however, infections, such as malaria, may occur in childhood and some immunity may be acquired in adults. Therefore, it may be appropriate to conduct clinical studies only in neonates and children in such areas.

For vaccine development, confirmatory phase III studies in consideration of the actual use conditions are conducted to obtain efficacy and safety data. In such a study, it is desirable to use the preventive effect of a vaccine as its endpoint. Since travelers' vaccines, etc. are preventive vaccines against infectious diseases that have not occurred or are rare in Japan, the implementation of a phase III study in epidemic areas should be considered in principle to obtain vaccine efficacy data.[1] The implementation of a study including Japanese people traveling to endemic areas can also be considered.

5. POINTS TO CONSIDER FOR CLINICAL EVALUATION

(1) Principles of efficacy evaluation

The efficacy of a vaccine is basically evaluated in a clinical study using its preventive effect as its efficacy endpoint. However, it is difficult to conduct a study to evaluate the preventive effect in Japan because such a study can be conducted only in a region where spontaneous infection is present at a certain prevalence and a comparative study can be conducted. Therefore, in principle, the efficacy of a travelers' vaccine, etc. should be evaluated and verified by conducting a randomized, double-blind, comparative study with an appropriate control group such as placebo using its preventive effect as its endpoint in the endemic area of the target infectious disease.[2]

For a travelers' vaccine, etc. whose preventive effect has been demonstrated in endemic areas, no confirmatory efficacy evaluation is required in a clinical study in Japan, but the necessity to confirm its immunogenicity using an indicator such as antibody titer should be considered.

When planning a Japanese clinical study to confirm the immunogenicity of a vaccine, consideration should include the vaccination schedule, route of administration, immunogenicity endpoints, etc. in the overseas clinical study that has demonstrated its preventive effect.

In some cases, a major difference in immune response may be expected due to differences in the distribution of the pathogen of the target infectious disease (e.g., strain, serotype, biological

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[1] If it is possible to obtain the results of a clinical study, such as a challenge study, which allows efficacy evaluation, it may be considered to explain vaccine efficacy based on such results.

[2] A study design without a placebo control group may be considered based on the mortality and seriousness of the disease.

type, phage type, genotype), the level of natural exposure, etc. between Japan and endemic areas. If the immune response is expected to be low or is not expected in Japanese people, it may be useful to confirm the immunogenicity in a Japanese clinical study using a larger number of vaccinations than the number of vaccinations evaluated in the clinical study in endemic areas.

(2) Efficacy evaluation of a travelers' vaccine, etc. for which there is a similar vaccine already approved in Japan

If there is a similar preventive vaccine against infectious diseases already approved in Japan, and there is an alternative indicator of immunogenicity whose relationship with disease prevention has been established, the efficacy of a travelers' vaccine, etc. may be explained by demonstrating its non-inferiority to the similar vaccine approved in Japan using the alternative indicator in a Japanese clinical study instead of evaluating its preventive effect in endemic areas.

6. POST-MARKETING INVESTIGATIONS

Travelers' vaccines, etc. also require formulation of a risk management plan. However, for a travelers' vaccine, etc. that is primarily administered to overseas travelers, it may be difficult to collect information in its post-marketing surveillance, etc. In such a case, it is necessary to consider collecting information by other methods, such as a method to effectively collect post-marketing information from overseas travelers, instead of conducting post-marketing surveillance, etc.

7. OTHER POINTS TO CONSIDER

(1) Simultaneous vaccination

When conducting a clinical study in Japan, it is desirable to obtain data on simultaneous vaccination that reflect the actual medical practice in Japan by taking into account vaccines expected to be administered simultaneously, such as routinely administered vaccines in Japan and other travelers' vaccines.

(2) Statistical considerations

For general statistical considerations in clinical studies, the "Statistical Principles for Clinical Trials"[4)] should be referenced.

(3) Assurance of quality

It should be noted that travelers' vaccines, etc. must meet the specification standards specified as monographs in the Minimum Requirements for Biological Products in order to obtain marketing approval.

LITERATURE REFERENCES

1) WHO. International travel and health, 2012.

2) "Guidelines for Clinical Studies of Preventive Vaccine for Infectious Diseases" (PFSB/ELD Notification No. 0527-5 issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare dated May 27, 2010)

3) "Guideline on the Development of Prototype Vaccine against Pandemic Influenza" (PFSB/ELD Notification No. 1031-1 issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare dated October 31, 2011)

4) "Statistical Principles for Clinical Trials" (PMSB/ELD Notification No. 1047 issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare dated November 30, 1998)

REFERENCE MATERIALS

(1) WHO. Guidelines on the quality, safety and efficacy of Vi polysaccharide conjugate typhoid vaccine, Draft, March 2013.

(2) WHO. WHO/BS/2012.2199:Guidelines on the quality, safety and efficacy of Japanese encephalitis vaccine (live, attenuated) for human use, Proposed Revision of WHO TRS No. 910 (Annex 3), Draft.

(3) WHO. WHO/BS/2012.2186:Guidelines to evaluate recombinant malaria vaccines targeting the pre-erythrocytic and blood stages of Plasmodium falciparum, Proposed guidelines, Draft.

(4) WHO. WHO position paper on hepatitis A vaccines – June 2012, Weekly Epidemiological Record No28-29, 87:261-276, July 2012.

(5) FDA. Guidance for Industry General Principles for the Development of Vaccines to Protect Against Global Infectious Diseases, December 2011.

(6) WHO. Vaccines against tick-born encephalitis : WHO position paper, Weekly Epidemiological Record No24, 86:241-256, June 2011.

(7) WHO. Recommendations for Japanese encephalitis (inactivated) vaccine for human use (Revised 2007), WHO Technical Report Series, No 963, Annex 1, 2011.

(8) WHO. Recommendations to assure the quality, safety and efficacy of group A meningococcal conjugate vaccines, WHO Technical Report Series, No 962, Annex 2,2011.

(9) WHO. Guidelines on the quality, safety and efficacy of dengue tetravalent vaccines (live, attenuated), Proposed replacement of Annex 1 of WHO Technical Report Series, No. 932, 2011.

(10) WHO. Rabies vaccines: WHO position paper, Weekly Epidemiological Record No32, 85:309-320, August 2010.

(11) WHO. Recommendations to assure the quality, safety and efficacy of live attenuated yellow fever vaccines, WHO Technical Report Series, No 872, Annex 2, 2010.

(12) WHO. Recommendations to assure the quality, safety and efficacy of recombinant hepatitis B vaccines, WHO Technical Report Series, No 786, Annex 2 and No 889, Annex 4, 2010.

(13) Menendez C. and Alonso P. Guidelines and considerations for testing malaria vaccines in pregnant women, Human Vaccines 6: 21-26, January 2010.

(14) IDSA. Immunization Programs for Infants, Children, Adolescents, and Adults: Clinical Practice Guidelines by the Infectious Diseases Society of America, Clinical Infectious Diseases 49:817–40, September 2009.

(15) WHO. Guidance on the evaluation of *Plasmodium vivax* vaccines in populations exposed to natural infection Vaccine 27: 5633–5643, July 2009.

(16) WHO. Proposed revision: Recommendations for Japanese Encephalitis Vaccine (inactivated) for human use, Expert Committee on Biological Standardization Geneva, 8-12 October 2007.

(17) WHO. Guidelines for the production and quality control of candidate tetravalent dengue virus vaccines (live), WHO Technical Report Series, No. 932, 2006 Annex 1.

(18) WHO. Guidelines for the production and control of inactivated oral cholera vaccines, TRS 924, 2004, Annex 3.