Administrative Notice
September 5, 2012

To: Division of Pharmaceutical Affairs,
Prefectural Health Department (Bureau)

From: Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Basic Principles on Global Clinical Trials (Reference Cases)

Promotion of global clinical trials is one of the key factors toward timely access of patients to new drugs.

In this regard, “Basic Principles on Global Clinical Trials” (PFSB/ELD Notification No. 0928010, Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 28, 2007) had been issued based on the knowledge accumulated through the clinical trial consultations of Pharmaceuticals and Medical Devices Agency.

Based on the outcome of cooperation in clinical trials among the regulatory authorities of Japan, China, and South Korea from 2007 as well as knowledge accumulated after the issuance of the above Notification, “Basic Principles on Global Clinical Trials (Reference Cases)” has been compiled as attached. Please notify related industries under the jurisdiction of this administrative notice.

Basic Principles on Global Clinical Trials (Reference Cases)

September 5, 2012
Pharmaceuticals and Medical Devices Agency

Introduction

Since the issuance of "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010, Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 28, 2007), Japan's participation in global clinical trials has been steadily increasing. In recent years, global clinical trials in East Asia (e.g., Japan, China and South Korea) have been increasing as well as those in the U.S. and Europe. The ways of cooperation between Japan and foreign countries has also been diversified. Specifically, Japan has been involved in global clinical trials at an early stage of drug development and large-scale global clinical trials in thousands of subjects. The regulatory cooperation among Japan, China and South Korea has also been reinforced as that among Japan, U.S. and Europe. In the current trend of global drug development, smooth and appropriate conduct of global clinical trials, especially in East Asia, is a critical issue not only for industries but also for regulatory authorities that evaluate study results.

In order to respond to these progress and changes, the Basic Principles on Global Clinical Trials (Reference Cases) has been developed. Based on recent cases, it intends to further promote an understanding of the former Notification in 2007 and ensure Japan's smooth participation in global drug development activities from an early stage as well as smooth and appropriate conduct of global clinical trials in East Asia where an increase in such trials is expected.

Since general considerations are provided for the reference cases listed below, it is recommended to utilize the clinical trial consultation with the Pharmaceuticals and Medical Devices Agency (PMDA) for individual cases.

The following recommendations are based on the current scientific knowledge. It should be noted that they may be reviewed and revised as needed, if situations change, science and technology advances, or evidence accumulates in the future.

1. Points to consider for global clinical trials in East Asia

(1) What are the special points to consider when conducting a global clinical trial in East Asia?	The types and frequency of metabolic enzyme polymorphisms and gene profiles are thought to be similar among East Asian ethnicities in Japan, China and Korea. Some drugs have recently been approved mainly based on the data from pivotal global clinical trials conducted in East Asia. Data from well-designed and conducted global clinical trials in East Asia is acceptable for documents of new drug application in Japan. However, the difference in ethnic factors (intrinsic factors as well as extrinsic factors such as local clinical practice and socioeconomic condition) may affect the efficacy and safety of drugs (effects not only on the data themselves but also on

	the evaluation; the same applies below as appropriate) even within East Asia. Global clinical trials conducted in East Asia need to be designed and conducted based on prior sufficient evaluation of the effect of ethnic difference on the efficacy and safety of drugs as in Japan-US-Europe global clinical trials. Especially when conducting a confirmatory trial in East Asian ethnicities by taking them as one population, the trial should be designed based on an appropriate hypothesis derived from considerations of sufficient data and information on the potential effect of differences between the Japanese and other East Asian ethnicities. Separate clinical pharmacology studies may provide useful data. It is recommended to consult on specific study design and evaluation methods with PMDA in advance. Further accumulation and review of scientific data and information on East Asian populations will deepen our understanding of ethnic differences and ensure a smooth and appropriate conduct of global clinical trials in this region. Such continuous efforts will improve the efficiency and quality of clinical development in East Asia and eventually facilitate the use of data from a global clinical trial including this region in new drug applications to be submitted to the Japanese regulatory authorities. Therefore, it is encouraged to consider to include global clinical trials to be conducted in East Asia as part of drug development plan and accumulate information.
(2) What therapeutic areas are recommended for global clinical trials to be conducted in East Asia?	A global clinical trial in East Asia can be performed for any target disease area. For diseases with high morbidity in East Asia (e.g., gastric cancer and hepatitis) of which conduct of confirmatory studies in Japan alone are difficult, proactive planning of a global clinical trial in East Asia may contribute to the improvement of the efficiency and quality of clinical development of a drug. Refer to the considerations described in Section 1-(1) above when developing a protocol. When planning global clinical development including East Asia and other regions such as the U.S. and Europe, the role of a clinical trial to be conducted in East Asia in the entire development plan should be defined in advance, and the activities in East Asia should be carried out in cooperation with those in the U.S. and Europe.
(3) What type of global drug development strategy can generally be planned based on data of interethnic comparison of pharmacokinetic profiles?	There is no general rule for a drug development strategy since it should be determined based on a variety of factors. If a drug development strategy aimed at regulatory approval in Japan is discussed based on pharmacokinetic (PK) differences of a drug among populations, comparison of the PK profile between Japanese and Caucasian or between Japanese and other East Asian populations will provide a useful information. If no marked PK difference is expected between Japanese and Caucasian populations, it will be useful to consider conducting a global clinical trial in Japanese and Caucasian populations from the early exploratory phase, followed by continuous global drug development in cooperation with the U.S. and European countries. When there is a marked PK

	difference between Japanese and Caucasian populations but not between Japanese and other East Asian populations, an East Asian exploratory clinical trial including Japanese and other East Asian population can be considered. In this case, drug development in East Asia will be a useful option. When there is a marked PK difference between Japanese and non-Japanese (Caucasian or other Asian) populations, a protocol should be developed based on thorough assessment of the reason for the difference and its effect on the efficacy and safety, and an exploratory study only in Japanese subjects should also be considered. Whether to conduct a confirmatory trial as a global clinical trial should be determined based on the result of prior exploratory studies. In addition to the difference in PK profiles, effects of ethnic factors affecting the efficacy and safety of a drug should be thoroughly evaluated by data from stratified analyses, etc. Prior to the confirmatory study, the appropriateness of setting and evaluating the treatment outcome in the overall study population as the primary endpoint needs to be explained. See "2-(6) What are the points to consider in evaluating the results of a global clinical trial?" for the evaluation of study results.
(4) Is it acceptable to conduct a bridging study not as a Japanese clinical trial but as a global clinical trial in East Asia and extrapolate the data from US/European studies to the Japanese population? If yes, what are the points to consider?	In Japan, a bridging study generally intends to extrapolate foreign data to the Japanese population and is conducted in Japanese subjects. To extrapolate US/European study data by conducting a global clinical trial in East Asia as a bridging study, sufficient data and information should be collected in advance to scientifically demonstrate that the ethnic difference between Japanese and other East Asian populations will not affect the data evaluation of the study. Furthermore, the consistency of the results between the Japanese and non-Japanese populations should be confirmed in such bridging study before the evaluation based on the bridging concept. For individual cases, it is recommended to consult with PMDA in advance. See the answer to the question #11 in the Questions and Answers of the ICH E5 Guideline ("Ethnic Factors in the Acceptability of Foreign Clinical Data"; Administrative Notice from the Evaluation and Licensing Division, Pharmaceutical and Safety Bureau, Ministry of Health, Labour and Welfare, dated October 5, 2006) for points to consider in conducting a global clinical trial designed as a bridging study.

2. General points to consider for global clinical trials

(5) What are the points to consider in planning Japanese clinical development strategies and a	An important point to consider a clinical development plan of a drug is to streamline and optimize the development process and protocols for subsequent phases during the course of drug development based on thorough and appropriate evaluation of data available so far, while developing a long-term and overall plan. Continuous consultation with PMDA

protocol of a Japanese study in the trend of globalization of drug development?	is recommended from an early stage. In the trend of globalization, global drug development may often be considered. It is recommended that coordination and cooperation with relevant foreign sections of the drug company be established and maintained regardless of the type of drug development strategy. The coordination and cooperation with relevant foreign sections include not only the conduct of a global clinical trial itself, but also involvement in protocol development, timely sharing of protocol and efficacy/safety data, and periodic correspondence regarding pharmaceutical regulatory affairs even in a case clinical trial is independently conducted in a foreign country or Japan. In other words, considerations based on accurate understanding and sharing of up-to-date data of a certain drug while cooperating with relevant foreign sections from an early stage will be the key to planning efficient and optimal drug development. To ensure appropriate drug development planning to obtain a marketing authorization in Japan, accumulation of data in Japanese subjects starting from an early, exploratory stage is recommended. There are currently three major types of clinical development strategies in Japan or multiple countries including Japan: single-country development, bridging development to which foreign data are extrapolated, and global development including confirmatory global clinical trials. The types of global development with the involvement of Japan may be divided into world-wide development conducted in cooperation with geographically distant countries such as the U.S. and European countries, and East Asian global development conducted in East-Asian countries such as Japan, China and South Korea. The characteristics of different development strategies should be thoroughly considered to develop an optimal protocol for the subsequent development phase based on the properties of the investigational drug and data available at the moment.
(6) What are the points to consider in evaluating the results of a global clinical trial?	The patient demographic information, efficacy, and safety should be evaluated in the same process as that used for a domestic study in Japanese subjects in principle. The consistency of the results between an overall study population and Japanese population based on sub-analysis should also be evaluated. It is important to consider the possibility that the Japanese population is a subgroup of the study and the sample size of the Japanese is generally insufficient to achieve the study objective, as well as the possibility that different results among different ethnic populations could be observed. When evaluating the data of a Japanese subgroup, the precision of the point estimate (e.g., standard deviation) should be taken into consideration as well as the point estimate itself based on the sample size of Japanese subjects. Furthermore, in addition to the evaluation of data in a Japanese subgroup for the primary endpoint, the results for the secondary endpoints in a Japanese subgroup should be evaluated to confirm a consistency with the results of primary endpoint and

	data in the overall study population. Similarly, whether there is a marked difference in the safety between an overall study population and a Japanese subgroup should be determined. If any difference is identified, whether the data from the global clinical trial can support the efficacy and safety of the drug in Japanese patients should be carefully evaluated based on thorough consideration of the reason for the difference by utilizing relevant data such as results of subgroup analysis for individual factors. The results of evaluation and discussion should be included in the Common Technical Document (CTD).
(7) What are the points to consider in evaluating the data of Japanese subjects living outside of Japan enrolled in foreign studies?	The (intrinsic and extrinsic) ethnic factors described in the ICH E5 Guideline should be considered to appropriately evaluate data from foreign studies. In early phase pharmacokinetic studies in Japanese subjects that usually enroll healthy adult volunteers, intrinsic ethnic factors such as genetic factors, rather than the local medical environment, are more important for the evaluation of study data. While extrinsic ethnic factors such as the living environment (e.g., diet) should be considered, data from foreign studies in Japanese subjects living outside of Japan are generally acceptable for the pharmacokinetic evaluation in the Japanese population. On the other hand, in studies to evaluate the efficacy and safety of a drug, extrinsic ethnic factors such as the local clinical practice (e.g., diagnostic methods and standard treatment) and social factors including education and culture as well as intrinsic ethnic factors need to be considered. The efficacy and safety in the Japanese population should be examined in the Japanese medical environment, i.e., based on the data from clinical studies (global clinical trials or domestic studies in Japan) that appropriately enroll Japanese subjects living in Japan.
(8) What are the general points to consider in comparing pharmacokinetic data between different ethnicities?	In general, interethnic pharmacokinetic (PK) comparison is recommended to be based on data collected according to the same protocol including measurement methods etc. (also applies to studies conducted separately) to minimize variations caused by non-intrinsic ethnic factors. If genetic variation in metabolic enzymes or transporters is expected to affect the PK of the investigational drug, genetic tests should be performed in the clinical trial to examine the incidence of genetic variation in different ethnicities and the PK-genotype relationship. Regarding the evaluation of PK similarities and differences among different ethnicities based on PK data from multiple independent studies, some cases have recently been reported where the data interpretation may be inaccurate unless extrinsic ethnic factors as well as intrinsic factors are taken into consideration (FY 2010 Health and Labour Sciences Research Grants, Research on Global Health Issue of Administrative Policy [Global Clinical Trial regarding Ethnic Differences in Drug Responses based on the Statement of Japanese, Chinese, and Korean Health Ministers]; The

	report of Kawai Study Group). Differences in measurement methods, specifically, clinical trial design, subject selection, quantitative tests (including validation status and detection limits), measurement time points, treatment condition, doses and dosage forms of the investigational drugs, standard deviations (including outliers), and timing of the study should be carefully evaluated. If differences are observed, the possible effect of the difference and its degree in the evaluation should be thoroughly examined before comparing data from multiple independent studies (bioequivalence should also be evaluated if different formulations are used). If no PK data are available from Japanese and non-Japanese subjects included in studies conducted under the same protocol, collection of PK data is recommended for parameters (e.g., C_{max} and trough level) appropriate in consideration of the characteristics of the drug at least at several time points in the major ethnic groups to be included in a confirmatory trial, at least before initiating a global confirmatory trial.
(9) What are the points to consider in conducting a phase I (First in Human) trial as a global clinical trial?	Active participation of Japan in global clinical trials from phase I with international cooperation is beneficial to collect useful information such as tolerability and pharmacokinetic data of Japanese subjects at an early stage without delaying the development schedule in Japan. When conducting a phase I trial as a global clinical trial, however, the safety of subjects in all participating countries and regions should be ensured, and adverse events that occurred at a study site and other practical concerns related to the trial should be immediately and appropriately shared among all study sites. Thus, whether to conduct a phase I trial as a global clinical trial should be determined based on comparisons of expected advantages and disadvantages of a global clinical trial with those of a domestic clinical trial. Moreover, since a phase I trial generally intends to evaluate the treatment tolerability in humans in a small sample size, only limited information and data can be obtained for the evaluation of ethnic similarities and differences in pharmacokinetics and pharmacodynamics. Therefore, interethnic comparison of data from a phase I trial as a global clinical trial will be recognized as an exploratory purpose. When taking above into consideration, it is appropriate to enroll Japanese subjects in the subsequent phases of the global clinical trial to further evaluate the effect of ethnic factors on the efficacy and safety of the drug. A separate clinical pharmacology study may be required when a marked interethnic difference may exist.
(10) When only a monotherapy study of an investigational drug was conducted in Japan, is it possible	In principle, data of the investigational drug in Japanese subjects who received the combination therapy with Drug A should be available before the participation in a global clinical trial. However, a global clinical trial investigating a combined use of the investigational drug may be conducted without data of its combination therapy with Drug A in

for the drug to be used in an exploratory global clinical trial including Japan investigating its combined treatment with Drug A?	Japanese subjects, if both of the following conditions are met: (a) based on results from foreign clinical trials or other studies, no increase of safety risks is expected when Drug A is used with the investigational drug and other drugs possibly used in the global clinical trial, and (b) the dose of Drug A has been used in patients in Japan for a certain period and its safety has already been established. For individual cases, it is recommended to consult with PMDA based on the scientific data and information available at the time.
(11) If the blood concentration of an investigational drug is different between Japanese and non-Japanese subjects (drug concentration in the Japanese is higher or lower than that in non-Japanese), is it acceptable to conduct an exploratory dose response trial as a global clinical trial including Japanese subjects, assuming that a certain number of Japanese subjects is enrolled and the safety evaluation is performed based on the drug safety profile and results of minimum examinations in the global clinical trial?	Whether to enroll Japanese subjects in an exploratory dose response trial as a global clinical trial when the pharmacokinetic data are markedly different between Japanese and non-Japanese subjects needs to be determined after thoroughly evaluating the mechanism of and reason for the difference, taking into consideration that the recommended clinical dose may potentially be different, and carefully comparing the advantage and disadvantage of a global clinical trial with those of a domestic clinical trial in Japan. For example, when the blood concentration of the investigational drug is higher in the Japanese population than that in non-Japanese populations, enrollment of Japanese subjects in a global exploratory dose response trial will be acceptable if the tolerability to the investigational drug in Japanese subjects has been confirmed based on the phase I trial and thorough safety measures will be taken in the global trial. In some cases, special safety monitoring in Japanese subjects may be required to adequately respond to adverse reactions. An appropriate range of study doses should be selected to include the recommended clinical doses in each ethnic group enrolled in the study based on thorough evaluation of existing data on pharmacokinetics and pharmacodynamics in Japanese and non-Japanese populations. It is appropriate that the sample size of Japanese subjects is determined according to the answer to question #6 in “Basic Principles on Global Clinical Trials” (PFSB/ELD Notification No. 0928010, dated September 28, 2007). However, the recommended clinical dose may be different between Japanese and non-Japanese patients when their pharmacokinetic profiles are markedly different. In such a case, the estimation of sample size is recommended to be conservative enough to thoroughly evaluate the dose response relationship in Japanese subjects while taking into consideration the study feasibility.
(12) If a drug has not been approved in Japan, is it acceptable to avoid assigning the drug as an active control to Japanese subjects in an	A global clinical trial should be conducted under the same condition that allows appropriate comparison of data from all participating countries and regions in the light of the study objective. A protocol should not include an active control group different from other participating countries only for Japanese subjects. Refer to the answer to question #9 in “Basic Principles on Global Clinical Trials” (PFSB/ELD Notification No. 0928010, dated September 28, 2007), describing that

exploratory study (use of an active control without assuring a statistical power for superiority or non-inferiority)?	the use of an unapproved drug as a control is acceptable if the drug is internationally established. The sponsor should obtain information on the control drug from package inserts in foreign countries and published literature to the extent possible and submit the information before initiating the trial. The sponsor should also establish a system to continuously collect and report safety information of the investigational drug as well as the control drug. In order to establish a system and procedures to exchange safety information on the control drug unapproved in Japan, the sponsor is recommended to consult with the relevant company which has the marketing authorization for the control drug in other countries in advance.
(13) What are the points to consider when the active ingredient of the active control drug has been approved in Japan and foreign countries but the dosage regimen or formulation is different?	A standard drug which is widely available is generally used as an active control to compare its efficacy and safety with those of the investigational drug. In general, the dosage regimen of the drug used as an active control in a global clinical trial is recommended to be within the range approved in the participating countries and regions. To ensure scientifically appropriate evaluation, the same dosage regimen should be used for the control drug in the participating countries and regions. However, the dosage regimen of a control drug may be different among the participating countries and regions in reality. The potential effect of the difference on the efficacy and safety should be thoroughly evaluated in advance. For example, if the approved dosage of the control drug is different between Japan and other countries, the reason for and background of the different dosage should be reviewed to evaluate the potential effect on the efficacy and safety. Specifically, different dose titration design may affect the early drop-out rate, and different maximum doses may affect the incidence of adverse reactions. For different formulations, the reason for and background of approval in the participating countries and regions should be reviewed, and the effect of different formulation on the dissolution profiles and blood drug concentration should be evaluated. The effect of using different dosage regimens or formulations in a study on the maintenance of blindness should also be evaluated. If such difference is expected to seriously affect the efficacy and safety, use of the drug as the control should be avoided. Conduct of a clinical trial in countries and regions where the dosage regimen and formulation approved in Japan can be used or use of other drug as the control should be considered. In some cases, if the dosage regimen has not been approved in Japan but recognized by international textbooks and medical guidelines and widely accepted in the Japanese clinical practice, the study dosage regimen may be determined in line with the internationally accepted dosage. For individual cases including the handling of the control drug, it is recommended to consult with PMDA.

(14) If a drug with different indications or dosage regimen depending on countries is used in combination with the investigational drug, can a global clinical trial be conducted?	The indications and dosage regimen of a concomitant drug may be different among countries and regions participating in a global clinical trial depending on the local clinical practice. The effect of the difference in the concomitant drug on the efficacy and safety of the investigational drug should therefore be thoroughly evaluated before selecting participating countries and regions. The dosage regimen of the concomitant drug in a global clinical trial should be consistent among the participating countries if the drug is likely to affect the efficacy and safety of the investigational drug, the concomitant use is unavoidable for the efficacy and safety evaluation of the investigational drug, and the prescribing information of the investigational drug needs to clearly specify the indications and dosage regimen of the concomitant drug (e.g., combination anti-cancer chemotherapy). When the indications or dosage regimen of the drug used in combination with the investigational drug is different among participating countries and region, a global clinical trial in the countries and regions can be still feasible, if such combination is not necessarily required but determined according to the patient's condition (e.g., hypnotics used in a study of depression), and if it can be explained based on a scientific rationale that the efficacy and safety of the investigational drug is not markedly affected. In such a case, however, the condition of the study should be consistent among the countries to the extent possible (e.g., dose change of concomitant drug is prohibited) to minimize the effect on the evaluation. Details and timing of treatment should be documented to allow later subgroup analyses to evaluate the effect of difference in use of the concomitant drugs on the efficacy and safety of the investigational drug.
(15) If the subject registration for a global clinical trial using a competitive registration system is completed before the target sample size of Japanese subjects is achieved, is a separate study in Japan required?	As stated in the answer to question #6 in "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010, dated September 28, 2007), the sample size of Japanese subjects to be enrolled in a global clinical trial should be determined to ensure the data consistency between the overall study population and the Japanese subgroup. Thorough assessment should be made in advance to achieve the originally determined sample size of Japanese subjects, and appropriate actions should be taken as necessary to achieve the objective based on careful monitoring of study progression. If the target sample size cannot be achieved despite every possible action, however, the sponsor should review the actions taken, the reason for the failure to achieve the sample size, and the data of overall study population and Japanese subgroup to determine whether the data consistency is demonstrated. A separate study may be required if data comparison between the overall study population and the Japanese population is difficult due to an extremely small number of enrolled Japanese subjects, or the data of overall study

	population and Japanese subgroup are inconsistent, suggesting ethnic differences and safety concerns. For individual cases, it is recommended to consult with PMDA.
(16) What are the points to consider in participating in a large-scale global clinical trial using a true endpoint such as survival time?	A large-scale clinical trial in thousands of subjects or more using a true endpoint such as survival time is often designed as a global clinical trial because of expected time required for case accumulation and other reasons. While Japan may contribute to establishment of evidence based on the true endpoint by participating in such a study, adequate sample size of Japanese subjects may not be achieved to evaluate the data consistency between the overall study population and the Japanese population, considering the large study scale and the number of participating countries and regions. Therefore, the sponsor should assess whether the overall study population including Japanese subjects can be deemed as a single population, based on thorough review of data on previously used endpoints, the association between the previous endpoints and the true endpoint, and the effect of international and interregional ethnic differences. Two ways to determine a target sample size of Japanese subjects are described in the answer to question #6 in “Basic Principles on Global Clinical Trials” (PFSB/ELD Notification No. 0928010, dated September 28, 2007). However, the proposed sample size determination is intended to be used for studies enrolling hundreds of subjects, and may be difficult to apply to larger-scale studies. While no established method of sample size determination is available for any study scale, in a large-scale study enrolling thousands of subjects or more, the use of a surrogate endpoint is an option to calculate minimum sample size of Japanese subjects for consistency evaluation, if the surrogate requires smaller sample size for evaluation and is reasonably associated with the primary endpoint (a true endpoint such as survival rate). In this case, the practical enrollment of Japanese subjects as many as possible over the minimum sample size is encouraged. Endpoints used in previous phase studies should be used as secondary endpoints in the protocol in addition to the endpoint used for sample size determination. Evaluation should be made not only based on the comparison of the primary (true) endpoint between the Japanese subgroup and the overall study population but also the secondary endpoints. Based on the information obtained from the clinical trial and the drug development program, whether the data of overall study population can be applied to the Japanese population should be explained.
(17) How many Japanese patients will be required for evaluating the long-term safety of a drug intended for long-term treatment of non-fatal disease, if	In the trend of globalization of drug development, active participation of Japan in global clinical trials is encouraged for efficient clinical development. However, when a drug is developed mainly based on global clinical trials, the total number of Japanese subjects included in the trial before the filing of the new drug application may be smaller than that in a case where the development is based on data from clinical trials conducted only in Japan. It potentially causes a problem in evaluating safety in the Japanese.

the data consistency has been shown between Japanese and non-Japanese subjects in a global clinical trial?	The long-term safety should be thoroughly evaluated for a drug for long-term treatment of non-fatal diseases. In general, safety data should be collected from approximately 100 or more Japanese subjects who have been treated for 1 year. However, in case of difficulty in enrolling subjects, a safety evaluation using data from trials not satisfying such number of subjects may still be possible in some situations, such as when Japan has been continuously involved in global clinical trials from an early and exploratory stage of drug developments and the data from multiple studies has not demonstrated any marked difference in safety between the Japanese and non-Japanese subgroups or when the drug has been approved in Japan for other similar indications and sufficient post-marketing safety data of Japanese patients has not demonstrated any marked difference from non-Japanese subjects. For individual cases, it is recommended to consult with PMDA.