September 28, 2007
Notification No.0928010

Attention to:
Commissioner of Prefectural Health Supervising Department

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

Basic principles on Global Clinical Trials*

Up to the present according to "Ethnic Factors in the Acceptability of Foreign Clinical Data" based on ICH-E5 guideline (Notification. No. 762, Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health and Welfare, dated August 11, 1998), utilizing foreign clinical trial data in a new drug application what is called "Bridging" has been accepted in Japan, and post-marketing data in USA and EU have been taken into consideration in a review for regulatory approval where necessary.

On the other hand, in the report entitled "Institutional reform for promoting science and technology and passing on the benefits of the scientific and technological advance" (Council for Science and Technology Policy, dated December 2006), it is mentioned to encourage global clinical trials in terms of efficient and rapid developments of new drugs. Moreover, in the final report of the special committee for "Effective & Safe Drugs Quick to Patients" (dated July, 2007), it is pointed out to promote global clinical trials in order to resolve "Drug lag (Circumstances where drug approved in EU and US are not approved in Japan and can not be provided to nations)" and to clear points to consider for conducting global clinical trials from the perspective of a review for regulatory approval.

Taking into account the situation, current understanding regarding global clinical trials based on experiences in PMDA consultations is outlined as the attachment, entitled "Basic principles on global clinical trials". We ask to inform manufacturers and sellers placed under your administration to utilize this for their business operations.

In addition, the copy of this notification is released to JPMA (Japan Pharmaceutical Manufacturers' Associations) and other related associations.

* This document is an informal translation by PMDA of the final notification published in Japanese on Sep. 28th 2007 and is intended to use as a reference for considering global clinical trials.

(Attachment)

Basic principles on Global Clinical Trials
(Final)

Introduction

Since the ICH E5 Guideline "Ethnic Factors in the Acceptability of Foreign Clinical Data" (Notification. No. 762, Director of Evaluation and Licensing Division (ELD), Pharmaceuticals and Food Safety Bureau (PFSB), Ministry of Health and Welfare (MHLW), dated August 11, 1998) was published in Japan, knowledge and experiences through using bridging strategies have been steadily accumulated with respect to how Japanese and foreign data can be appropriately evaluated depending on type of drug, targeted disease area, and global status of clinical development. Recently, by making use of these knowledge and experiences, sponsors have increasingly employed a drug development strategy from the early stage of development which includes conducting global clinical trials. In these circumstances, drug development strategies taken in Japan are expected to be further diversified.

Currently, the Japanese "drug lag" problem, a several years' delay of new drug approval in Japan from foreign countries, has been aggravated. To substantially solve the "drug lag" problem, it is necessary to synchronize drug development timings in Japan with those of other countries. A possibly effective approach for it would be for Japan to participate in global clinical trials from an early stage of the drug development. If this approach will encourage Japanese drug development and eliminate the "drug lag", effective and safe drugs can be made available to Japanese patients without a delay from the rest of the world. It would greatly contribute to improving the level of drug therapy and public health in Japan.

To promote global clinical trials including Japan, since FY2006, the Pharmaceuticals and Medical Devices Agency (PMDA) has given priority status to sponsors' requests for clinical trial consultation on global clinical trials. It is important that sponsors and PMDA sufficiently discuss the clinical study design and data handling, etc. for individual development programs through the clinical trial consultations, assuming conduct of a global clinical trial. To make this possible, it has been responded through the clinical trial consultations. Based on cases in the past clinical trial consultations, basic principles for design and conduct of global clinical trials have been discussed and clarified.

This paper describes basic principles for global clinical trials including Japan and will promote further consideration by sponsors as well as active participation for Japan in global clinical trials.

The issues in this paper were considered based on current scientific knowledge. It should be noted that the principles may be reviewed and revised as needed if situations change or science and technology advances in the future.

Scope

Although this paper is mainly intended for drugs to be newly developed, some issues in this paper are also applicable to drug development cases for which some degree of data have been obtained in the non-Japanese from phase II or III studies already completed in foreign countries.

Basic Principles

Since a global clinical trial, different from a domestic clinical trial, is performed across different regions and ethnicities, it is necessary to take ethnic factors into account when planning clinical trial. Accordingly, considering issues described in the ICH E5 Guideline is also useful for planning a global clinical trial. The bridging concept can be applied not only to cases where development in other countries precedes that in Japan, but also to simultaneous development as in the case of global clinical trials. Also see the question #11 in the Questions and Answers of the ICH-E5 Guideline (Office Communication of ELD, PMSB, MHLW, dated October 5, 2006), which clearly describes this concept.

Basic principles for the design and conduct of global clinical trials are provided in the following Q&As, but these principles and optimal development strategies may differ by individual drug. For individual cases, issues identified in this notification, such as development strategies and trial designs, should be considered in advance, and the clinical trial consultations with PMDA should be utilized as soon as possible.

In addition, "global clinical trial" defined in this notification is a trial designed for a new drug aiming for worldwide development and approval, having multiple countries, regions and medical institutions participating in a single clinical trial and conduct concurrently in accordance with a common clinical trial protocol.

1. What are the basic requirements to conduct a global clinical trial?

All of the following requirements need to be satisfied:

- The clinical trial can be conducted in compliance with the ICH-GCP in all participating countries and clinical trial sites, etc.
- All the participating countries and clinical trial sites can accept GCP audit from Japan.
- Along with prior consideration regarding factors (race, region, patient demographics, etc.) that may affect to the efficacy and safety of an investigational drug, subgroup analysis based on relevant factors can be possible to achieve and appropriate considerations should be provided.
- Social differences such as customs, and practical situations such as control and management of clinical trials in each trial sites can be properly understood, and appropriate considerations if the

observed differences could affect to trial results can be provided.

2. What is an appropriate timing for Japan to participate in global drug development?

Regarding clinical developments that are globally proceeding, it is recommended to participate as soon as possible. Therefore, prior consideration is important so that, at the latest, participation to the exploratory dose-finding study could be possible.

3. Is it mandatory to have a phase I trial or pharmacokinetic information in Japanese population prior to conduct of a global clinical trial for patients?

The dosage regimen to be used in the global trial should be confirmed beforehand as to whether it does not have any particular safety problem for the Japanese. For this purpose, before the start of the global clinical trial, at least it is required to examine single dose safety and pharmacokinetics of investigational drugs in Japanese healthy volunteers or patients, compare the results with non Japanese, and confirm that risks in the Japanese are equivalent with non Japanese.
However, if safety in the Japanese can be determined from the results of phase I trials conducted in a foreign country, or if a recommended dose for both Japanese and non-Japanese can be judged similar from situations of similar drugs, or if there are other appropriate reasons, a phase I trial in the Japanese is not necessarily required prior to the global trial. But even if it is the case, because a comparison between the Japanese and non-Japanese as to how the pharmacokinetics relates to the clinical effects would be still useful in determining an appropriate dose for the Japanese, and also it could be considered as an important information when interpreting the results of a global clinical trial, it is recommended to include the results in the new drug application document by conducting an appropriate clinical pharmacology study in parallel with the global clinical trial if necessary, or examining relationships of pharmacokinetics and clinical effects in the global clinical trial.

4. Is a development program acceptable in which Japanese subjects are included only from a confirmatory phase III trial using a dose determined based on results from non-Japanese clinical trials, without conducting any dose-finding study in Japan?

Such a program is not appropriate from the standpoint of the primary goal, which is to deliver effective and safe drugs to Japanese patients. Based on the approved applications over the past years and our review experiences based on the ICH E5 Guideline, pharmacokinetics may be different between Japanese and non-Japanese, and it is sometimes difficult to conclude that a recommended dose determined based on a non-Japanese clinical trial results is also a recommended dose for

Japanese.

Therefore, to facilitate drug development and reach regulatory approval in Japan at the same time as approvals overseas, it is recommended to include Japanese patients into a dose-finding study to identify inter-ethnic difference in dose-response relationship early in clinical development, and subsequently design a confirmatory study. Even in the cases of different recommended doses between the Japanese and Caucasians, if it can be explained adequately that the different doses in different regions yield an equivalent efficacy and safety, the results from the subsequent phase III global trial (a confirmatory trial) in each region can be combined and handled as results of the primary analysis population.
Also note that, in cases when there are similarities in the PK (pharmacokinetics), and correlation between PK and PD (pharmacodinamics), which has a clear relation with clinical effects, are shown, dose-finding study based on a clinical effect in Japanese is not always necessary.

Note:
In some areas including orphan drugs, or drugs for life-threatening diseases for which established treatment are not available, it may be sometimes difficult to conduct a domestic dose-finding study. In such cases, some measures should be considered such as performing phase III trials under strict monitoring by physicians.

5. What are the basic points to consider in designing a global clinical trial?

The basic points to consider are provided below. For more details also see the question #11 in the Questions and Answers of the ICH-E5 Guideline.

- In case of conducting a global clinical trial, it is necessary to evaluate effects of ethnic factors specific to individual regions on efficacy and safety of the investigational drug and efficacy and safety of investigational drugs in Japanese.
- It is necessary that designs and analytical methods for the global clinical trial should be acceptable to Japan.
- The primary endpoints should be those acceptable to all individual regions. If the primary endpoints are different by region, data on all the primary endpoints should be collected in all regions so that inter-regional difference can be examined.
- To allow for appropriate safety evaluation, the collecting and assessing method of adverse event information should be standardized as much as possible across all regions.

6. When conducting an exploratory trial like a dose-finding study or a confirmatory trial as a global clinical trial, how is it appropriate to determine a sample size and a proportion of Japanese subjects?

- In a global trial, sample size can be calculated assuming results from the entire study population across regions. In this case, a sufficient statistical power to detect statistically significant difference should not necessarily be secured within the Japanese subpopulation. However, when the entire study population across regions is defined as a primary analysis population in a confirmatory study, the justification should be explained as to why the entire population can be deemed as one population, while each regional population is not used.
- If results from a Japanese subgroup are markedly different from those in the entire study population, the reasons for it should be examined and in this case, because an additional clinical trial may be needed where necessary, it is recommended to utilize the clinical trial consultation with PMDA.
- A global trial should be designed so that consistency can be obtained between results from the entire population and the Japanese population, and by ensuring consistency of each region, it could be possible to appropriately extrapolate the result of full population to each region.
- Therefore, since no method has been currently established as generally recommendable to calculate a sample size, it needs to be determined by considering some factors, including the number of regions to be included, the scale of trial, target disease, and the relevant ratio between the total and Japanese subject numbers. To consider the possibility to obtain consistent results between the entire population and the Japanese population when designing a global trial, taking as an example a placebo-controlled study using quantitative endpoints, the following methods can be applied:
  (1) *Method 1:* Suppose that difference between placebo and study drug groups is D, then the difference in the entire study population across regions is D_{all}, and the difference within the Japanese sub-population is D_{Japan}. Determine the number of Japanese subjects so that $D_{Japan}/ D_{all} > \pi$ will occur with a probability of 80 % or higher. A π should be set as an appropriate value, and 0.5 or more is generally recommended. When this method is used, the following relationships will be observed: An attempt to minimize the Japanese sample size will increase the total sample size, and an attempt to minimize the total sample size will increase the Japanese sample size.
  (2) *Method 2:* Suppose that difference between placebo and study drug groups in the entire study population across regions is D_{all} , and if assuming that three regions are included in the trial, the differences between placebo and study drug groups in each region are D_1, D_2, and D_3, respectively. Determine sample sizes so that each of the D_1, D_2, and D_3 show a

similar tendency. For example, in the case of D>0, the number of subjects is determined so that each of the D_1, D_2, and D_3 will exceed 0 with a probability of 80 % or higher. The probability tends to increase if equal number of subjects is enrolled from each region. This method allows considering the Japanese sample size without changing the total sample size. However, it should be noted in this method that sufficient interregional comparison may not be possible when Japanese component ratio is small and number of subjects are few.

Reference:

For example, assume conduct to a few hundred subjects of a two-arm, placebo-controlled parallel group study in which the efficacy is similar across regions. For a scientifically appropriate evaluation based on the study results, (1) by the *method 1*, if attempting to minimize the Japanese sample size while to an adequate extent preventing increase of the total sample size, Japanese subjects are needed to account for about 20 %; (2) by the *method 2*, when conducting a trial in three regions, with the power of the trial as 90 % for the total sample size, Japanese subjects are needed to account for about 15 % or more.

Note:

Specific sample size setting for individual cases can be discussed with PMDA on the clinical trial consultation.

7. There may be cases where a global trial has to use an evaluation index which has been established overseas but not established in Japan. In such a case, can the index be also acceptable in Japan?

If such a case is expected, conduct of a pilot study in Japan or other appropriate measures would be needed at as an early stage as possible, to confirm whether drug response in the Japanese is similar to those obtained from foreign clinical studies. In addition, to minimize possible differences among raters, trial sites, and regions, some measures are needed before the start of the study, such as developing and conducting a regionally-common training program. It should be noted that, in such situations as in this question, participation in a global trial without any consideration for the evaluation in Japanese will not yield appropriate results in Japan, and furthermore, may adversely affect the entire study itself.

8. If a global trial has been performed outside Japan and the identical protocol is used for a smaller clinical study separately performed in Japan, can it be justified to conclude that the efficacy and safety are the same in both Japan and outside Japan based on the results of these studies?

If a global clinical study has been performed outside Japan and the results are to be analyzed separately from those in a Japanese study, they should generally be regarded as separate trials. In such a case, on the condition that the given primary endpoint is appropriate, it would be appropriate to plan/conduct a prospective bridging study with enrollment of enough number of subjects to allow statistical consideration within the Japanese, and to consider the difference from the results of non-Japanese clinical study based on the ICH E5 Guideline.

9. Regarding control groups in a phase III confirmatory global trial:

(1) There are cases of global trials which use only placebo groups as control. Even in such a case, is it required in Japan to include an active control group?

(2) There are cases where the active control drug is an international standard, but not approved in Japan. In such a case, how should a control drug in Japan be determined?

(1) In principle, that is not required. It is appropriate to design a global trial so that superiority over placebo can be demonstrated and consistent results can be obtained across regions. If there are available results from an independent study using an active control drug, they would help clarify in some cases the clinical positioning of the investigational drug. But since clinical positioning may be explained by other methods, conduct of such a study is not automatically required.

(2) A drug that is not approved in Japan can be used as active control for a global clinical trial, if the active drug can be objectively explained to be an international standard from descriptions in foreign guidelines or other relevant documents. However, prior consideration is necessary on how such unapproved drug can effect to the Japanese, especially regarding safety. Since results from a non-inferiority study with an unapproved drug need careful interpretation, it is recommended to consider in advance the extrapolability of study results to Japanese patients by gathering information as much as possible regarding efficacy and safety data of the unapproved active drug and especially on the differences between approved drugs in Japan and the unapproved active drug.

10. In a global trial, it is difficult to define the use of concomitant medications or therapies in a completely identical manner between Japan and other countries. How can these be appropriately defined?

Since it is difficult to provide general answers for cases of various types of concomitant medications

or therapies, two examples are described here.

In either case, sufficient considerations associated to individual cases are necessary regarding validness of dosage and administration of the concomitant medication. On that condition, when the grounds of the intended global clinical protocol largely relies on the evidence from foreign countries, basically it is theoretical to conduct domestic clinical trials using the same concomitant medications and therapies, and also this can lead to enhance the success rate of the trial.

(1) In the case of a combination of drugs when both have high toxicity and narrow therapeutic ranges like anticancer drugs, it is recommended to apply a strictly identical dosage regimen in both Japan and other countries.

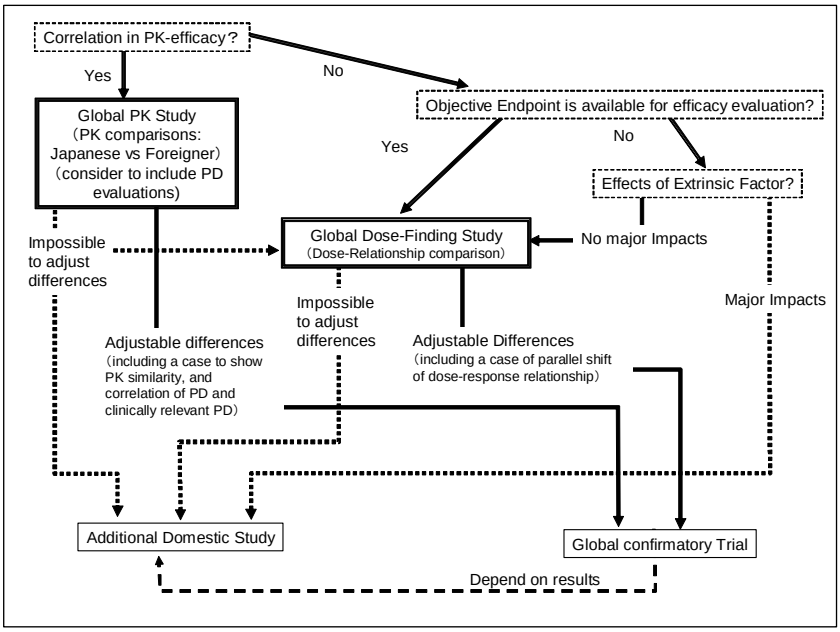
(2) For normally combined drugs or treatment as a standard therapy, it may be assumed difficult to uniform regulations of dosage and administration of each region. In this case minimum differences could be acceptable, but considerations should be given to minimize the possible influence that the difference may have upon investigational drug's efficacy and safety. The consideration would include maintaining a constant dosage of the concomitant within each subject throughout the trial period including a prior observation period.

11. Are there any disease areas where conduct of a global trial is recommended?

A global clinical trial can be performed in any therapeutic areas. But among others, for diseases for which conduct of a large confirmatory clinical trial in Japan will be difficult, e.g., orphan diseases, conduct of a global clinical trial should be actively considered. Although there have been study cases in Japan where drugs are experimentally used in a small number of subjects to gain some experience, more recommended development strategy for Japan is to enroll as many Japanese subjects as possible in a global trial, and thereby build clinical evidence based on the more appropriately designed trial. Also, in other cases than orphan diseases, conduct of a global clinical trial should be considered when it is assumed to take a long time to accumulate a sufficient number of subjects even at global level, such as a large clinical trial that needs to enroll thousands of subjects and use true clinical endpoints (e.g., survival rate). In such cases, it would be a possible approach for Japan to actively participate in it and contribute to establishment of evidence. By applying this kind of strategy, eventually it is considered that equal timing of new drug application for each region may be possible.

12. Is there a reference flow chart for determining whether or not a global clinical trial should be performed?

As there would be many exceptions and no universal approach exists, it would be appropriate to determine conduct of a global trial on a case-by-case basis. But at present, the flow chart presented below would provide a general approach.



The questions in the dotted boxes (⬚) in this chart show issues that may also be confirmed by other study results, such as results of other preceding studies on the same disease. The judgment whether or not there is an important difference or effect should be made taking into consideration the design of the clinical studies, the comparison between populations, and other relevant factors.